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THE TREATMENT AND PROPHYLAXIS OF SUBACUTE BACTERIAL ENDOCARDITIS

RAY A. VAN OMMEN, M.D.
Department of General Medicine

SUBACUTE BACTERIAL ENDOCARDITIS is one of the important bacterial diseases which has been transformed from a uniformly fatal disease to one with a favorable outlook for cure since the era of antibiotic therapy. It is, however, an exceptional and perhaps unique disease in relation to the task that chemotherapy has to perform. Although the prevention of further bacterial growth by antibiotics and the subsequent disposal of surviving organisms by the natural defenses of the body are sufficient to eradicate most bacterial infections, they apparently are not sufficient in subacute bacterial endocarditis. The clinical course of the disease prior to the antibiotic era showed that host factors are incapable of eliminating this type of infection. To prevent relapse, chemotherapy must eliminate the last surviving organisms from the endocardial focus.

Consideration of the pathology in this disease helps us to understand the obstacles that antibiotics must surmount in order to eradicate this infection. The organisms are buried in fibrin and in scarred, avascular, necrotic tissue. To effect a cure, an agent with fibrin-penetrating and bacteria-killing properties must be present in high concentrations over an adequate period of time. It is, therefore, not surprising that bactericidal drugs are indicated in this disease rather than those that are bacteriostatic in their action. Both clinical and laboratory evidence[1] indicate that the presence of bactericidal action is a prerequisite for the cure of subacute bacterial endocarditis.

In the treatment of this condition the failure of sulfonamides was early evidence that bacteriostasis in addition to host factors was incapable of curing this disease. Temporary remission of symptoms and control of bacteremia were observed, but relapse almost invariably occurred after the drugs had been

discontinued. Much the same experience has been noted with the use of the newer bacteriostatic agents, such as chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol, although cures have been accomplished in some patients treated with these drugs. Penicillin and streptomycin, which have bactericidal properties, remain the primary drugs in the treatment of subacute bacterial endocarditis.

It must be kept in mind that the routine sensitivity tests reported from the laboratories measure only the bacteriostatic or inhibitory action of a drug and give no true indications of its bactericidal or actual killing activity. Therefore, though the laboratory report shows that an organism responsible for a case of subacute bacterial endocarditis is highly sensitive to one of the bacteriostatic drugs, clinical experience indicates that these are not the drugs of choice and a bactericidal agent should be used.

The Organisms and the Choice of Drugs

The nonhemolytic streptococci are responsible for about 95 per cent of all cases of subacute bacterial endocarditis. The remaining 5 per cent of the cases are caused by a number of different organisms, many of which are penicillin-resistant gram-negative bacteria, and therapy for these cases has to be individualized (Table 1).

Table 1.—*Organisms causing subacute bacterial endocarditis*

I. Nonhemolytic streptococci	
A. *Streptococcus viridans*	85 to 90% of cases
1. *S. salivarius*	
2. *S. mitis*	
3. *S. s.b.e.*	
B. Enterococci	5 to 10% of cases
1. *S. faecalis*	
2. *S. liquefaciens*	
3. *S. zymogenes*	
II. Multiple other organisms, such as Brucella, diphtheroids, *Hemophilus influenzae, Pseudomonas aeruginosa, Escherichia coli, Proteus vulgaris*, fungi, yeasts	5% of cases

The nonhemolytic streptococci are of two important groups: (1) *Streptococcus viridans*, and (2) the enterococci. *Streptococcus viridans* continues to be the most common offender in this infection and accounts for up to 90 per cent of all cases due to nonhemolytic streptococci. Fortunately they are usually sensitive to penicillin in the range of 0.1 or less unit per cubic centimeter in vitro, and daily doses of 2 to 2½ million units are sufficient for cure in most cases. The enterococci which make up the remaining 5 to 10 per cent of the cases caused by nonhemolytic streptococci, however, present a more difficult therapeutic

problem. These cases may frequently be therapeutic failures because the enterococci are extremely resistant to penicillin in the range of 1 to 5 or more units per cubic centimeter.

Large doses of penicillin alone—10 to 50 million units daily—have been successful in the treatment of some of the enterococcal infections. However, since the combination of penicillin and streptomycin has been demonstrated to have a synergistic effect on the enterococcus,[2,3] the daily use of large doses (10 to 20 million units) of penicillin with 1 to 2 gm. of streptomycin appears to offer a much better chance for cure. There is evidence that a combination of penicillin and bacitracin also has a synergistic action,[4,5] and it has been used successfully in the treatment of these enterococcal infections.[6] Large doses of penicillin are administered with 60,000 to 100,000 units of bacitracin daily. This combination may be used when there are contraindications to the use of streptomycin, or if a substitution for streptomycin is necessary because of toxic reactions. Bacitracin is a potentially nephrotoxic agent and must be used with care when employed over long periods of time.

The 5 per cent of cases of subacute bacterial endocarditis due to a wide variety of organisms other than nonhemolytic streptococci require individual consideration for the selection of the drug or combination of drugs to be employed. Streptomycin is used in the treatment of many of the gram-negative organisms. A combination of streptomycin and chlortetracycline appears to be the treatment of choice for the Brucella organisms. In rare cases caused by *Pseudomonas aeruginosa*, the use of polymyxin B may be necessary. At times one may have to resort to a trial with the broad-spectrum antibiotics in some infections due to rare organisms that are entirely unresponsive to penicillin or to streptomycin. There is no effective treatment for endocarditis caused by fungi or yeasts.

Methods of Treatment

Although the penicillin-sensitivity studies indicate only the inhibitory action of the drug, they nonetheless are of considerable practical value in estimating the daily dose necessary in the individual case (Table 2). However, this table can be considered to be only a guide, for if the clinical response is not satisfactory the theoretically desirable dose must be increased rapidly and progressively.

Table 2.—*Suggested dosage schedule in relation to the in vitro sensitivity of the organism in units per cubic centimeter of penicillin*

Sensitivity, units per cc.	Penicillin, units per day
0.05 to 0.1	2,000,000
0.1 to 0.2	3,000,000
0.2 to 0.5	4,000,000
0.5 to 1.0	8,000,000
1.0 to 5.0	10,000,000 to 20,000,000
5.0 to 10.0	20,000,000 to 40,000,000

After three or four blood cultures have been taken during a 48 to 72 hour period, a schedule of penicillin treatment may be instituted, such as 2 to 2½ million units of aqueous or procaine penicillin G each 24 hours in divided doses. After the organism has been identified and the sensitivity studies have been completed the dose may be altered as necessary and streptomycin added if an enterococcus is isolated.

In the treatment of highly resistant organisms that require more than 10 to 12 million units of penicillin daily, the intramuscular route of administration may become impractical and the continuous intravenous route may be more satisfactory. Intravenous administration can be conveniently accomplished by using a small polyethylene tube that is anchored in a vein and allows the patient complete freedom of movement in bed with little chance of subcutaneous infiltration. Aqueous penicillin is added to the infusion bottle along with 50 mg. of heparin, and 1000 ml. of this solution is allowed to drip in slowly over each 12-hour period. In this manner, almost unlimited amounts of penicillin can be used.

The use of a drug that inhibits the excretion of penicillin is occasionally desirable when treating an organism that is moderately or highly resistant to penicillin. Probenecid (Benemid, Merck, Sharp & Dohme), in doses of 0.5 gm. every six hours, may double the blood level of penicillin. Fortunately, probenecid does not inhibit the excretion of streptomycin and it can be given without fear of increasing the chances of streptomycin-toxicity reaction.

Sensitivity reactions to penicillin occasionally may complicate the therapy. If they occur during treatment one must resist the temptation immediately to substitute an agent that has only bacteriostatic action, as such a change will compromise the chances of cure. Every effort should be made to continue the use of penicillin. The minor skin reactions frequently can be controlled by the use of antihistaminics. The substitution of penicillin O for penicillin G may readily solve the problem.[7] Occasionally, the employment of corticotropin (ACTH) may permit the continuation of the essentially needed penicillin in the presence of allergic reactions.

When streptomycin is given daily over long periods of time it may have toxic effects. The insidious loss of hearing caused by dihydrostreptomycin would seem to be more serious than the vestibular damage that streptomycin may produce and, therefore, the latter should be used initially. If vestibular symptoms develop, which often are transient, the change may be made to dihydrostreptomycin. This method appears to be safer than using a mixture of the two drugs, in spite of evidence suggesting that the use of the two forms in a 1:1 ratio may reduce toxicity to the eighth cranial nerve.[8]

Duration of Treatment

In the early days of antibiotic therapy for subacute bacterial endocarditis it was believed that six to eight weeks of treatment was indicated. However, about four weeks of treatment has proven to be sufficient in most cases. In recent years

investigation has been directed toward shortening the period of treatment. In 1952, Hamburger and Stein[9] reported that cases caused by penicillin-sensitive *Streptococcus viridans* were successfully treated with doses of 15 million units of penicillin daily for two weeks. Geraci and Martin[10] reported that of 23 patients having subacute bacterial endocarditis due to penicillin-sensitive *Streptococcus viridans*, 18 were cured with moderate doses of penicillin combined with dihydrostreptomycin over a two-week period. It appears likely that the administration of this combination of drugs is satisfactory treatment in selected cases in which the diagnosis has been made early in the course of the disease, and in which the organism has proved to be *Streptococcus viridans* and is highly sensitive to penicillin (0.1 or less unit of penicillin per cubic centimeter). Four weeks of treatment should be used for more penicillin-resistant *Streptococcus viridans*, for all enterococci, and for organisms other than the nonhemolytic streptococci.

Results of Treatment

The results of therapy have been reported many times in recent years, with over-all recovery rates ranging from 65 to 80 per cent. Recovery rates vary according to whether the rate represents only patients who have had bacterial cure, or also includes those patients who, within a few weeks or months after bacterial cure, die from congestive heart failure that was not present prior to the onset of the disease.

It has been demonstrated that healing of the valvular veruccae by fibrosis and endothelialization requires several weeks or months.[11] The additional scarring and retraction of previously diseased valves then may increase the mechanical insufficiency of the heart and result in cardiac decompensation. This complication is particularly apt to be a serious sequela when the aortic valve is involved. To minimize this additional valvular damage, early diagnosis of subacute bacterial endocarditis is important, so that treatment can be instituted before a larger section of the valve becomes involved in the infectious process. Delay in diagnosis and inadequacy of treatment are the primary factors that increase mortality. Factors of lesser influence are the age of the patient, the resistance of the organisms, and the type of predisposing cardiac disease.

Prophylaxis

The ideal form of therapy for most bacterial disease, and certainly for subacute bacterial endocarditis, is prevention. Since bacteremia is essential for the organisms to progress to the endocardium, measures should be taken in all susceptible individuals to prevent bacteremia. There are innumerable sources of bacteremia, with tooth extractions being the most familiar source as related to subacute bacterial endocarditis. However, cases of endocarditis are believed to have been caused by many other operative and diagnostic procedures, particularly those involving the genitourinary system and the oral cavity. Other predisposing factors have been abdominal operation, bronchoscopy, abortion,

and spontaneous delivery. In general it may be said that entrance of organisms into the blood stream may be facilitated by any operation or diagnostic instrumentation that traumatizes a mucosal surface exposed to bacteria.

The routine prophylactic treatment in the past has consisted of the administration of 600,000 to 1,000,000 units of procaine penicillin G a few hours prior to dental or other surgical procedures, and of a similar daily dose for three or four days postoperatively. The simultaneous injection of 600,000 units of aqueous penicillin and 600,000 units of procaine penicillin in oil containing 2 per cent aluminum monostearate 30 minutes before an operative procedure may be adequate for complete protection without need for additional doses. A dependable oral preparation, such as penicillin V, in doses of 200,000 to 400,000 units every six hours, beginning 24 hours prior to surgery and continuing for five days, should provide adequate protection. The bacteriostatic antibiotics also have been shown to be effective in controlling bacteremia[12] and can be used safely as prophylactic agents, even though they are predominantly ineffective after the endocardial infection has become established.

Summary

1. Bactericidal action appears to be essential to the cure of subacute bacterial endocarditis; bacteriostatic agents are largely ineffective.

2. Penicillin is the preferred drug in therapy for the largest group of cases, those that are due to *Streptococcus viridans*. The best treatment for subacute bacterial endocarditis due to the enterococci is the combination of large doses of penicillin with streptomycin.

3. Methods of treatment and prophylaxis are discussed.

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OCULAR MANIFESTATIONS OF SARCOIDOSIS

MARVIN F. GREEN, M.D.,* AND ROSCOE J. KENNEDY, M.D.
Department of Ophthalmology

OCULAR lesions occur in approximately 50 per cent of patients having sarcoidosis. It is the purpose of this paper to review these manifestations, to discuss their possible diagnostic significance and their treatment, and to summarize the findings in 11 patients.

Sarcoidosis is a ubiquitous disease of unknown etiology. Although it has received much attention in the literature of the past 50 years, no specific therapeutic agent has yet been found. In 1948 the Committee on Sarcoidosis of the National Research Council of the United States[1] defined sarcoidosis as:

> . . . a disease of unknown etiology. Pathologically it is characterized by the presence in any organ or tissue of epithelioid cell tubercles with inconspicuous or no necrosis and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The lesions may be replaced by fibrosis, hyalinization or both. Clinically, the lesions may be widely disseminated. The tissues most frequently involved are the lymph nodes, lungs, skin, eyes, and bones (particularly of the extremities). The clinical course usually is chronic with minimal or no constitutional symptoms. However, there may be acute phases characterized by malaise or fever. There may be signs or symptoms referable to the tissues and organs involved. The intracutaneous tuberculin test is frequently negative. The plasma globulins are often increased. The outcome may be clinical recovery without radiographically visible residue or there may be impairment of the organs involved, or a continued chronic course of the disease.

Sarcoidosis affects young adults of both sexes. Most reports indicate that Negroes are more susceptible than white people, in ratios up to 16:1.[2] It has been observed in persons in all parts of the country; however, Michael, Cole, Beeson, and Olson[3] found in a follow-up of 226 patients (both white and Negro), originally reported by Ricker and Clark,[4] that most of the patients had come from the southeastern section of the United States.

A characteristic feature of sarcoidosis is the lack of direct correlation between the severity of symptoms and the extent of involvement. The general health of the patient often is good, although he may lose some weight and have febrile periods. Almost any part of the body may be affected. The lungs most frequently are involved and roentgenograms show a reticular infiltration that is most pronounced near the hili, and an increased hilar shadow resulting from hilar lymphadenopathy. There may be enlargement of other lymph nodes throughout

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From the Lower Prize Fellowship Thesis by Doctor Green for The Frank E. Bunts Educational Institute.
**Formerly Fellow, also Assistant Staff Member of the Department of Ophthalmology. Present address: 2307 Northwest Overton, Portland 10, Oregon.*

the body. Involvement of the bones, usually the phalanges, results in punched-out cystlike areas or in a lattice-like diffused involvement. Disseminated nodules may appear in the skin—most often in that of face, forearms, neck, shoulders, and legs. Similar nodules may occur in nerves, pleura, pericardium, prostate, skeletal muscles, spleen, liver, and kidneys.

Laboratory studies frequently show a reversal of the albumin-globulin ratio in the blood plasma. There sometimes are an increased sedimentation rate, a slight rise in blood calcium, and a mild eosinophilia. Some patients have false-positive blood Wassermann reactions. Most patients have anergy to tuberculin; whether this is an actual entity or is only a factor of epidemiology was questioned by Michael and associates.[3] Of the 226 patients mentioned previously, most came from rural areas where one would expect a greater percentage of the population to show anergy to tuberculin.

The most recent and helpful aid in the diagnosis of sarcoidosis is the Kveim test,[5,6] in which the patient receives an intracutaneous injection of specially prepared macerated sarcoid lymph node. In patients with active sarcoidosis the injection causes the formation of a fresh sarcoid nodule which is biopsied and examined histologically about six weeks after injection. The Kveim test also may be used to determine the progress of the disease: when the disease is in remission, the test is negative.

Ocular Manifestations

Sarcoidosis may affect almost any portion of the eye, but the uveal tract is most frequently involved. Woods[7] reported that the eyes were involved in 44 per cent of 94 patients. Longcope[8] found ocular involvement in 16 of 31 patients (23 of whom were Negroes); in 12 of the 16, the ocular involvement was the first manifestation of the disease. The uveal tract was involved in 13 patients, the cornea in 5, the conjunctiva in 2, and in 1 patient each, the sclera, the retina, the choroid, and the optic nerve. Uveoparotid fever also was present in 7 of the 16 patients. In a review of 100 patients with sarcoidosis reported by other authors, Levitt[9] noted that 43 patients had ocular lesions. In this group the uveal tract was involved in 28 patients of whom 10 had phthisis bulbi, the lacrimal glands in 9, the lids in 7, and the conjunctiva in 6.

The following is a description of the manifestations of sarcoidosis in the eye and its adnexa.

Uveal tract. Inflammation of the anterior uveal tract is the most frequent ocular manifestation of sarcoidosis. There is no relationship between the onset of the ocular inflammation and that of any other manifestation of the disease. The iritis usually is painless, inflammatory symptoms are slight, and synechia is common. The typical clinical picture is that of a nodular type of iritis. The nodules usually are superficial, but may lie deep in the stroma. The nodules of sarcoid are said to be larger, more pink, more irregular, and more vascular than true miliary tubercles. It is questionable that the type of vascularization of the nodule in sarcoidosis is pathognomonic, as it differs little from that of the tubercle in tuberculosis. However, in sarcoidosis the vessels form an interlacing pattern in and over the nodule, whereas in tuberculosis the vessels pass over and

around the tubercle and invade the surrounding iris.[7] The large keratic precipitates of the "mutton-fat" type also are typical of sarcoidosis. On occasion there may be considerable inflammation with the development of a heavy plastic iritis. If the parotid gland becomes swollen, Heerfordt's disease (uveoparotid fever) develops. There also may be cranial nerve palsies, especially of the facial nerve. Walsh[10] has observed transient palsies of all the cranial nerves except the eleventh and twelfth.

Lacrimal glands. Sarcoidosis may produce a painless swelling of one or both lacrimal glands. The enlarged gland is not attached to the skin and is of firm, somewhat nodular consistency. Often there is an associated involvement of the submaxillary and salivary glands and of cervical lymph nodes producing Mikulicz's disease.

Conjunctiva. Lesions of the conjunctiva are comparatively rare. Small nodules or large follicles may occur in the palpebral conjunctiva, bulbar conjunctiva, or cul-de-sac. The lesions are grey, yellow-brown, or yellow-red, and are firm, painless, and movable.

Lids. On the lids cutaneous lesions may occur which exactly duplicate those on other parts of the body. Small, painless, firm, subcutaneous nodules that histologically are typical of sarcoid also may occur. These lesions may be the only manifestation of the disease or they may be associated with other lesions.

Cornea. It is doubtful that sarcoid nodules ever occur primarily in the cornea; corneal lesions usually are in association with uveitis. In such cases the lower part of the cornea is most frequently involved with a descemetitis and an interstitial keratitis.

Sclera. Although involvement of the sclera has been reported, Woods[7] states that there is no evidence of true scleral involvement in any of the reported cases.

Fundi. Sarcoid lesions of the fundi are comparatively rare. Yellowish nodules of the choroid have been observed. Walsh[10] observed in a patient a choroidal mass of 8 diopters in the left eye, bilateral optic atrophy, and small retinal masses. Periphlebitis may accompany the retinal lesions.

Findings in 11 Cases

Our findings in 11 patients having ocular manifestations of sarcoidosis are summarized in the table. The ages ranged from 21 to 70 years, but seven patients were from 21 to 32 years of age. Six of the patients were women, and five were men. Three of the patients were Negroes (two women and one man).

Laboratory findings. Most of the laboratory results were typical of sarcoidosis. Anergy to tuberculin was demonstrated in eight of the nine patients tested; the result in one patient was not recorded. The Kveim test was positive for sarcoidosis in six of the nine patients tested; the result was negative in two; it was not recorded for one patient. In one of the patients whose test was negative the sarcoidosis was thought to be in a state of remission; in the other patient it was found that a weak, equivocal antigen had been used. Abnormalities, consisting most frequently of a hilar adenopathy, were present on the roentgenograms of the chest of 10 of the 11 patients. There was a reversal of the albumin-globulin ratio in four of six patients tested. The blood eosinophil counts for five patients were: 0, 2, 3, 4, and 6 per cent, respectively. The sedimentation rate studied in five patients was increased in two, equivocally increased in two, and normal in one. The blood Wassermann test was negative in all 11 patients.

Ophthalmologic findings. As in all other published reports the uveal tract was the portion of the eye most frequently affected. Ten of the patients had

Table. — *Data for 11 patients having sarcoidosis*

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Patient's				Laboratory findings								Treatment	
Patient no.	Sex	Race	Age, yr.	Tuberculin	Kveim test	Albumin: globulin ratio	Eosinophil, %	Sedimentation rate	Serology	Roentgen findings in chest	Ocular manifestations	Local	Systemic
1	F	W	29	–					Negative	+	Heerfordt's disease (uveoparotid fever), superficial keratitis, cysts of the iris	Atropine and merthiolate ointment	None
2	M	W	29	–		Normal	4	Increased(?)	Negative	+	Iritis	Unknown	Irradiation to chest
3	F	W	24	–	+				Negative	+	Heerfordt's disease (uveoparotid fever), superficial keratitis	Atropine	Calciferol
4	M	W	42	–	+		2	Increased	Negative	+	Heerfordt's disease (uveoparotid fever)	Atropine	Calciferol
5	F	W	53	–	–	Reversed	6		Negative	+	Iritis	Cortisone and atropine	Nitrogen mustard
6	F	W	43	–	?	Normal			Negative	+	Iritis	Cortisone and atropine	Cortisone orally
7	F	N	25	?	+	Reversed		Normal	Negative	+	Iritis, secondary glaucoma	Cortisone and atropine; paracentesis	Cortisone and ACTH, followed by isoniazid
8	M	N	27	–	+	Reversed	3	Increased	Negative	+	Iritis	Cortisone and atropine	Isoniazid followed by cortisone
9	F	N	32		+				Negative	+	Papules on lids, inactive iritis, old descemetitis, keratitis	Zinc and Adrenalin drops	Isoniazid
10	M	W	21	–	+	Reversed	0	Increased	Negative	+	Right eye: old chorioretinitis. Left eye: large mass covering disc	None	Cortisone, ACTH, isoniazid
11	M	W	70		–				Negative	–	Iritis	Cortisone and atropine	Isoniazid

evidence of an anterior uveitis that was active; three of these also had Heerfordt's disease (uveoparotid fever).

Treatment and results. The patients were treated during the past seven years, and accordingly the changes in treatment reflect the therapeutic progress of the period. In the table the cases are listed in chronologic order according to the date of initial examination. The patient seen earliest (Patient 1) received no medication for her systemic disease. Atropine and merthiolate ointment were recommended for topical treatment of her eyes, but she was examined only once, and the results of treatment are unknown. Two of the other early patients received calciferol. It is not known what treatment, if any, Patient 2 received for iritis. The only known systemic therapy was irradiation to his chest administered in another hospital to prevent the development of Hodgkin's disease. For Patient 3 atropine alone, topically applied to the eyes, gave excellent improvement in the severe iritis. (This patient was one of identical twins, both of whom had sarcoidosis but the other twin had no ocular manifestations. The case was reported by Rogers and Netherton.[11]) In Patient 4 it was recommended that the pupils be kept dilated with atropine, but the results are not known.

In five patients (5, 6, 7, 8, and 11), most recently seen, iritis was treated by topical application of cortisone and atropine. In each, the iritis subsided although there was mild recurrence in some patients. Patient 5 obtained a remission of her generalized disease after a course of nitrogen mustard therapy. Patient 6 received cortisone orally and since then has had no systemic manifestations of the disease. Patient 7 received a short course of cortisone orally and corticotropin (ACTH) intramuscularly, followed by a longer period of isoniazid therapy orally; her condition also improved. For Patient 8 the administration of isoniazid was stopped after two months when he developed iritis; the oral administration of cortisone and the local application of cortisone and atropine were begun and the patient became symptom-free. Patient 11 now is receiving only isoniazid systemically, and the skin lesions are disappearing.

The condition of Patient 10 who has the large mass involving the optic disc has not yet shown any improvement. He received cortisone, ACTH, and isoniazid systemically. It would seem that the extent of involvement is too great to hope for any appreciable restoration of function of the optic nerve.

Discussion

Patients having iritis who demonstrate anergy to tuberculin, possibly may have sarcoidosis; however, if the iritis is definitely granulomatous, the possibility of the presence of sarcoidosis is even greater. In such cases a Kveim test should be performed in addition to study of the plasma proteins and routine diagnostic measures such as roentgen study of the chest and differential blood count. A biopsy of lymph nodes also occasionally may be advisable. Some form of therapy should be started before the results of the Kveim test are known, since the test requires six weeks.

At present, there is no specific therapeutic agent for sarcoidosis. Many types

of therapy have been used, including administration of chaulmoogra oil, sulfones, antibiotics, vitamins, nitrogen mustard, calciferol, dihydrotachysterol, phototherapy, and irradiation. These measures have been replaced by the administration of isoniazid and cortisone, which seem at the present time to offer the best form of treatment. However, Patient 8 developed iritis after taking isoniazid for two months for systemic sarcoidosis. Increased tendency to bleed also has been reported as occurring in some patients being treated with isoniazid.[12,13] Wacker and Bonard[12] noted an increased coagulation time in one third of the patients and clinical manifestations of increased tendency to bleed in some of the patients receiving isoniazid. Schlaegel and Hungerford[13] believe that isoniazid may have aggravated the hemorrhagic tendency of some of the fundal lesions in their patients. One of our patients without ocular manifestations of sarcoidosis (not included in this series), after four weeks of treatment with isoniazid, developed retinal hemorrhages as a part of isoniazid intoxication. Certainly one patient represents a very small percentage of the number of patients who have been treated here with isoniazid during the past few years. The possibility exists, however, that other patients may have had hemorrhages that went undetected because they were too small or too few to cause visual disturbances, and therefore funduscopic examinations with mydriasis were not performed.

Schlaegel and Hungerford[13] administered isoniazid to one patient having tuberculous uveitis. Although there was a definite but delayed improvement in the patient's condition, the authors proposed that the favorable response might have been a coincident spontaneous improvement.

The iritis caused by sarcoidosis probably is best treated by local applications of cortisone and atropine. This treatment resulted in remission of the iritis in all five patients to whom it was administered in this series (Patients 5, 6, 7, 8, and 11). Dahlene[14] reported that local application of these drugs in combination with oral administration of cortisone resulted in dramatic improvement in vision of one patient having sarcoidosis with iritis. Ozazewski and Bennett[15] compared the results of treatment in three patients having sarcoidosis. No improvement in vision occurred in one patient who received a total of 360 mg. of corticotropin, or in another patient who received a course of old tuberculin followed by a total of 100 mg. of urethan. However, there was pronounced improvement in vision of the third patient who received a total of 240 mg. of corticotropin systemically and cortisone locally: vision improved from nil to 20/70 in the right eye and from light perception to 20/30 in the left eye.

Some mild exacerbations of the iritis have occurred in our patients and in those reported by others who were treated with cortisone and atropine, but "rebound phenomenon" never has occurred. Rebound phenomenon—severe exacerbation when cortisone therapy is stopped—has been observed in patients having tuberculous ocular disease.[16]

Summary

Approximately 50 per cent of the cases of sarcoidosis are associated with

ocular manifestations, most of which occur in the uveal tract. Of 11 patients having sarcoidosis, 10 had involvement of the uveal tract (inactive in only 1), 3 of whom had Heerfordt's disease (uveoparotid fever). Three patients also had corneal involvement secondary to the uveitis, and one patient had typical skin lesions on the eyelids. The one patient not having manifestations in the uveal tract had extensive involvement of the optic disc in one eye and of the choroid and the retina in the other.

The topical application of cortisone and atropine to the eye seems at the present time to be the most effective treatment of anterior uveitis resulting from sarcoidosis. However, the patients also should receive treatment for the systemic manifestations of the disease.

In a patient having a granulomatous type of uveitis who demonstrates anergy to tuberculin, sarcoidosis may be present. It is recommended that in such a patient special diagnostic tests, particularly the Kveim test, be performed in addition to the routine diagnostic measures.

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COBALT-60* TELETHERAPY FOR COMPLICATED PEPTIC ULCER

A Preliminary Report

CHARLES H. BROWN, M.D.,
Department of Gastroenterology

and

ROBERT A. HAYS, M.D.
Department of Radiology

ROENTGEN THERAPY to the fundus of the stomach was first used 40 years ago by Bruegel[1] in the treatment of peptic ulcer. Palmer and associates[2-4] have used irradiation extensively during the past 20 years as one aspect of ulcer therapy that included a strict medical regimen consisting of a bland diet, frequent feedings, antacids, sedation, psychotherapy, and other measures. In 1948 they[3] reported follow-up studies on 800 patients, and to date approximately 1200 of their patients with peptic ulcer have received such therapy.[2] Their follow-up studies have revealed excellent results, with a low incidence of recurrent peptic ulcer, which have stimulated our interest in the adjunctive use of irradiation in the treatment of complicated peptic ulcer.

Gastric secretory studies are most important in evaluating any treatment for peptic ulcer. It has been repeatedly stressed, "No acid, no ulcer." Any type of therapy that results in anacidity will be effective ulcer treatment. In 1939, Palmer and Templeton[4] reported a transitory reduction in acid secretion in all cases receiving roentgen therapy. In 35 of 88 patients studied, achlorhydria occurred. Ricketts, Kirsner, Humphreys, and Palmer[5] found a reduction in volume of gastric secretion averaging 47.5 per cent, with complete anacidity in 13 of 15 patients with gastric ulcers who had received a depth dose of 1600 r. With their latest technic (Technic A) and with a depth dose of 1600 to 2500 roentgens, 44 (76 per cent) of 58 patients developed achlorhydria, and an additional 6 (11 per cent) had a 50 per cent or more reduction in acid secretion. They [2-4] found that larger doses of irradiation were more effective in producing anacidity. This effect of different doses was further indicated in the report by Brown and associates[6] that in only 3 of 12 patients anacidity followed irradiation with 1500 r, but in 6 of 10 patients anacidity followed irradiation with 2000 r. All of these secretory studies have shown that: (1) Irradiation results in depression of gastric secretion and frequently in anacidity. (2) There is correlation between

**The radioactive material used in this study was supplied on authorization of the Isotopes Division, United States Atomic Energy Commission, Oak Ridge, Tennessee.*

the degree of reduction of acidity and the amount of irradiation administered. (3) The decrease in acid secretion may persist for varying periods. (4) While the acid secretion remains depressed, the ulcer heals and does not recur.

Technics of irradiation. Various technics of irradiation have been used. McGeorge[7] used radium needles in the stomach, giving 2000 to 3000 milligram-hours. Sixteen of his 32 patients developed achlorhydria, while 28 of 30 patients showed reduction in the amount of free acidity, and 29 of 30 had reduction in volume of secretion. Brown and associates[6] initially used only roentgen irradiation in 22 patients. Of 10 patients who received 2000 r, 4 had severe relapses (3 required surgical treatment). Subsequently, these investigators combined roentgen with surgical (antroduodenectomy) therapy in 10 patients. The preliminary results of combined irradiation and surgical treatment were excellent in the limited follow-up period of three months. A much longer period of follow-up, as the writers point out, is necessary for proper evaluation. Four technics of roentgen therapy have been used by Palmer and associates.[2,3] With their latest technic[2] a barium swallow outlines the stomach fluoroscopically so that irradiation may be directed at the upper two thirds of the stomach in which there is the greatest concentration of acid-secreting cells. The depth doses are 1600 to 2500 r through two portals, anterior and posterior.

Ricketts, Palmer, Kirsner, and Hamann[3] in an analysis of 800 cases of peptic ulcer treated in the years 1936 to 1947, reported that the recurrence rates of gastric and duodenal ulcer were lower in the group of patients that had received roentgen therapy than in the group that had not received irradiation. They concluded that, in the treatment of peptic ulcer, irradiation of the acid-secreting portions of the stomach was a valuable procedure, the effect being proportional to the reduction in gastric secretion. As they further indicated, the use of radiation therapy for peptic ulcer is based on the concepts of the relationship of acid gastric secretion and chronic peptic ulcer, and the depressant effect of roentgen irradiation on gastric secretory capacity.

Since September 1954, irradiation with the cobalt-60 teletherapy unit has been used at the Cleveland Clinic. The present report is based on the results of administering cobalt-60 teletherapy to 15 patients having complicated peptic ulcer. We believe that this is the first report on the use of cobalt-60 teletherapy for this purpose.

Technic

In general we have followed the procedure that was originated by Palmer and his group[2-4] for the administration of roentgen irradiation to the stomach for peptic ulcer. However, instead of the usual 200- or 250-kv. roentgen ray machines, we use a cobalt-60 teletherapy unit (equivalent to 3000 kv. or 3 million volts).

The patient is given a small amount of barium orally, and is fluoroscoped in both the prone and supine positions. The upper two thirds of stomach is outlined on the skin while the patient is in the prone and supine positions since these are the positions he will assume on the therapy table.

Two fields, one anterior and one posterior, centered over the upper two thirds of the stomach, are employed. This effectively cross-fires the acid-bearing portion of the stomach. From 1600 to 2000 r to the stomach were given through these two portals to each of our 15 patients (Table 1). We space the treatments fairly closely, giving 300 r to the skin of each of the two fields daily for six to eight days.

Table 1.—*Effect of cobalt-60 teletherapy on gastric acidity*

Diagnosis	Case no.	Dose of Co^{60}, r	Gastric acidity: Before therapy, units	Gastric acidity: After therapy, units	Decrease in free HCl, %	Length of time since therapy
Duodenal ulcer	1	1600	102/114	10/36	90	8 wk.
	2	1664	74/90	12/22	89	6 wk.
	3	1600	110/122	00/26	100	8 wk.
	4	1800	109/121	24/56	88	6 wk.
	5	1840	22/32	00/12	100	8 wk.
	6	1600	90/112	50/68	44	8 wk.
	7	1700	60/72	40/62	37	3 wk.
	8	1800	98/110	58/74	43	8 wk.
	9	1800	120/136	14/24	88	9 wk.
	10	1800	92/108	20/30	78	8 wk.
	11	2000	114/126	76/90	32	8 wk.
Marginal ulcer	12	1600	68/82	62/72	10	6 mo.
	13	1600	Not determined			
	14	2000	46/62	00/18	100	8 wk.
Gastric ulcer	15	2000	118/128	14/28	89	8 wk.

The cobalt-60 teletherapy unit has certain physical advantages over the conventional roentgen ray therapy machines. In particular, it has a skin-sparing effect and, being more penetrating, a greater depth dose is obtained. We believe that there is no difference between the biologic reaction to the gamma rays of cobalt-60 and that to the roentgen rays of a 250-kv. roentgen ray machine. In the average patient, measuring approximately 22 to 24 cm. in anteroposterior diameter, a 50 per cent depth dose at 11-cm. depth is obtained with the cobalt-60 equipment. To deliver 2000 r to the desired portion of the stomach, 2000 r must be administered to the skin of each of the two fields. This dose together with an exit dose of approximately 600 r means that the skin fields receive approximately 2600 r, but no noticeable skin reactions have resulted. A similar amount of conventional roentgen irradiation would cause a mild

erythema. We consider that with benign conditions we are not justified in giving treatment that can cause a skin reaction, particularly in patients of the younger age group.

In addition to cobalt-60 teletherapy, the patients were treated medically as outlined by Brown and Hoerr.[8] They were given a generous, bland diet that includes meat and cooked vegetables and between-meal food or milk every two hours from arising to retiring, antacids on the odd hours when they were awake, mild sedation in the form of phenobarbital, and one of the anticholinergic drugs.

The patients were not hospitalized, but were given the teletherapy as outpatients. Although hospitalization offers rest and a beneficial change in environment to a patient with peptic ulcer we believe that, given adequate instruction, he can adhere to his medical program of hourly feedings or antacids carefully at home.

Selection of Patients

The 15 patients selected for cobalt-60 teletherapy had not responded to previous medical treatment, had evidence of complications of peptic ulcer or of intractability, and were considered to be possible candidates for operation. Surgical treatment was not advised or performed because of various contraindications such as cardiac disease, or because of the reluctance of the patient to undergo operation. Operation was cancelled for one patient when he became cyanotic on the operating table before any surgery. Cobalt-60 teletherapy was given in addition to the medical treatment in the hope that operation might be avoided.

The duration of ulcer distress ranged from 2 to 30 years, with an average of 12 years of intermittent ulcer pain (Table 2). Six of the 15 patients had had one episode of massive bleeding, and one had had three episodes of minor bleeding. Three patients had obstruction and vomiting, and a fourth patient had obstruction with a dilated stomach and no vomiting. Eleven of the patients had duodenal ulcer. Of three patients with marginal ulcer, two had had two operations for peptic ulcer previously (Table 2, Cases 12 and 14).

Results

Pretreatment and posttreatment white-cell counts and hemoglobin determinations showed no significant change.

Clinical response. The clinical response of peptic ulcer to any type of therapy is difficult to evaluate because of our limited knowledge of the natural history of untreated peptic ulcer, and the latitude in patient self-treatment and professionally administered therapy. In cases of duodenal ulcer many patients undoubtedly treat themselves, with or without the help of the local druggist, using measures such as control of diet and doses of soda and proprietary antacids. Probably only those patients with stubborn or complicated ulcers who

Table 2. — *Response to cobalt-60 teletherapy in 15 patients having peptic ulcer*

Diagnosis	Case no.	Duration of symptoms, yr.	Symptoms	Previous surgical treatment	Response to cobalt-60 teletherapy	Length of follow-up, mo.
Duodenal ulcer	1	27	Pain, vomiting	None	Asymptomatic	4
	2	7	Pain, hemorrhage, melena	None	Asymptomatic	3
	3	2	Ulcer distress, melena	None	Asymptomatic	4
	4	10	Obstruction, pain, melena	None	Asymptomatic	4
	5	14	Pain, vomiting, melena	None	Asymptomatic	4
	6	10	Pain, hematemesis	None	Asymptomatic	2½
	7	5	Pain, vomiting	None	Asymptomatic	2
	8	2½	Recurrent ulcer	None	Asymptomatic	2
	9	30	Recurrent ulcer	None	Asymptomatic	2
	10	3	Pain, not working for 9 mo.	None	Asymptomatic	2
	11	8	Pain, melena	None	Asymptomatic	2
Marginal ulcer	12	10	Severe pain	Gastric resection, Jan. 1953; vagomy, Aug. 1953	Asymptomatic	8
	13	15	Pain, 3 episides of melena	Vagotomy and gastroenterostomy, 1952	Asymptomatic	16
	14	15	Pain, requiring narcotics	Gastrojejunostomy, 1947; vagotomy, July 1956.	Asymptomatic	2
Gastric ulcer	15	15	Recurrent pain	None	Asymptomatic	2

have not responded to home remedies or to treatment by their local doctors are referred to medical centers. Consequently, the group that is seen in large clinics is a selected one. In addition, irradiation is not used alone, but is combined with other types of therapy, such as diet, frequent feedings, antacids, sedation, antispasmodic and anticholinergic drugs, and psychotherapy, and it is therefore difficult to evaluate the effect of irradiation alone.

The long histories of ulcer in the group, the number of complications, and the lack of response to previous medical (in three cases also surgical) treatment are some measure of control. Follow-up periods have been short, ranging from 2 to 16 months. During this time the symptomatic response has been satisfactory in every case (Table 2). In each patient there has been relief of ulcer distress, and no further hemorrhage or other complications.

Gastric acidity. Gastric analyses, using Histalog (3-beta-aminoethylpyrazole dihydrochloride) as a stimulant, were obtained before and after irradiation in 14 of 15 patients. According to Kirsner, Levin, Palmer, and Ford,[9] Histalog is

Chart.—*Per cent decrease in free HCl after cobalt-60 teletherapy*

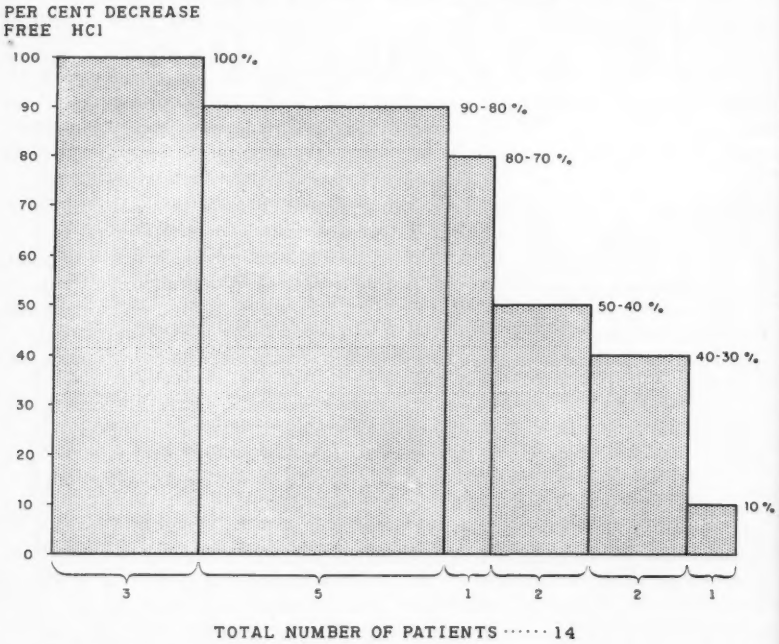

Chart depicting the percentage decrease in free hydrochloric acid after cobalt-60. All gastric analyses were done with Histalog as a stimulant. From the chart it can be seen that 8 of 14 patients had an 80 per cent or greater reduction in free hydrochloric acid.

entirely comparable to histamine in stimulating gastric-acid secretion. Fifty milligrams (one ampule) of Histalog was given to each patient in a fasting state. The results of the analyses are summarized in Table 1.

Thirteen of the 14 patients had an appreciable reduction in gastric acidity, greater than 32 per cent. Nine of the 14 patients had a reduction in gastric acidity of more than 75 per cent (Chart). Anacidity was produced in three patients. More frequent gastric analyses after irradiation might have shown a higher incidence of anacidity, since this anacidity frequently is temporary. Gastric analysis could not be obtained in Patient 13 (Table 1) until six months after irradiation, when it showed little change. However, the marked symptomatic improvement in this patient suggests that he had at least a temporary decrease in acidity. Despite the small number of patients and of determinations of secretory response, we believe that these studies show that irradiation with cobalt-60 may appreciably decrease gastric-acid secretion.

Roentgen findings. Progress roentgen examinations were made of 13 patients (all except Cases 6 and 13, Table 3). In each the ulcer crater disappeared.

Table 3.—*Roentgen findings before and after cobalt-60 teletherapy*

Diagnosis	Case no.	Roentgen findings		Length of time after therapy
		Before therapy	After therapy	
Duodenal ulcer	1	Crater	Deformity only	2 mo.
	2	Crater	Deformity only	6 wk.
	3	Crater	Deformity only	2 mo.
	4	Crater, obstruction	Deformity only	10 wk.
	5	Crater, obstruction	Deformity only	2 mo.
	6	Crater	Not available	——
	7	Crater	Deformity only	2 mo.
	8	Large ulcer crater	Crater healed	9 wk.
	9	Crater	Less deformity, no crater	9 wk.
	10	Large crater	No crater	8 wk.
	11	Crater	Crater healed	8 wk.
Marginal ulcer	12	Large marginal ulcer	Normal stoma	2 mo.
	13	Crater	Not available	——
	14	Large marginal ulcer	Normal stoma	8 wk.
Gastric ulcer	15	Crater, lesser curvature of antrum	Crater healed	8 wk

Side effects of therapy. Twelve of the 15 patients tolerated the therapy without side effects. Three patients had minimal nausea but no vomiting while undergoing therapy. The degree of nausea was much less in these patients than in those who, prior to the use of cobalt-60, were given comparable doses or

roentgen irradiation to the stomach for peptic ulcer. No skin changes were noted in any of the patients.

Discussion

Gastric secretory studies in 14 of the 15 patients having peptic ulcer showed a reduction in acidity in 13 after cobalt-60 teletherapy (1600 to 2000 roentgens). This reduction was greater than 75 per cent in 9 of the 14 patients. Our experience supports that of other investigators who showed that with larger doses of irradiation a greater depression of acid secretion results. For further studies we plan to give approximately 2000 roentgens.

The effect of roentgen therapy can be measured directly by determining gastric-acid secretion. Frequent gastric-acid determinations will aid in estimating both the expected response to the treatment and the possible value of cobalt-60 teletherapy for all patients having ulcer. We are planning follow-up studies that will include gastric-acid determinations every two months for the first six months after irradiation, and twice yearly thereafter.

Histologic findings. The histologic findings after irradiation have been reported by several investigators.[5-7,10] Ricketts and associates[5] reported gastroscopic and gastric biopsy findings after irradiation in patients having peptic ulcer. Goldgraber and associates[10] made extensive studies of three patients undergoing roentgen therapy for duodenal ulcer. With a modified Wood biopsy tube, they performed 40 biopsies within a four-month period. The histologic changes were of a patchy nature. Initially, coagulation necrosis of the fundal glands occurred, involving both the chief and the parietal cells. At the peak of reaction, there was partial to complete loss of glandular substance, with mucosal thinning, edema, and chronic inflammatory infiltration of the mucosa. The reversion to normal was complete and prompt. Brown and associates[6] evaluated the response to irradiation on the basis of 138 gastric biopsies with the Wood instrument. McGeorge's[7] findings were similar: an initial necrosis followed by an inflammatory reaction in five patients who had undergone gastrectomy after irradiation.

Gastric ulcer and cobalt-60 teletherapy. In this study, we have included only one patient having gastric ulcer. Patients with gastric ulcer have less acid secretion than do those with duodenal ulcer. Levin and associates[2,11] found that postirradiation anacidity develops more frequently and that irradiation produces better results in patients with gastric ulcer than in those with duodenal ulcer. We are planning to study the effects of this type of therapy on more patients with gastric ulcer.

Summary

The results of administering cobalt-60 teletherapy to the stomach in 15 patients having peptic ulcer are encouraging. The doses ranged from 1600 to

2000 r and were well tolerated causing no skin changes or other side effects, except minimal nausea. Since irradiation with cobalt-60 is better tolerated than is the conventional roentgen treatment, it is suggested that irradiation with cobalt-60 is preferable. Gastric-acid secretion was significantly reduced in 13 of 14 patients, and 3 of the 14 developed anacidity.

There was a good symptomatic response in all patients. Before cobalt-60 teletherapy, all 15 patients had symptoms of complicated peptic ulcer and had not responded to medical treatment. The good symptomatic responses strongly suggest that irradiation was beneficial.

Progress roentgen examinations in 13 patients showed the ulcer craters to have disappeared within 6 to 10 weeks after irradiation.

The results of this short-term experience indicate the desirability of further use of cobalt-60 teletherapy as an adjunct to the treatment of patients with peptic ulcer resistant to other medical regimens.

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OBSERVATIONS ON ARTERIAL HOMOGRAFTS WITH SPECIAL REFERENCE TO PATHOLOGIC CHANGES

A Preliminary Report

WILLIAM A. HAWK, M.D.,
Department of Pathology

and

ALFRED W. HUMPHRIES, M.D.
Department of Vascular Surgery

ARTERIAL HOMOGRAFTS offer a bright promise to those patients who have advanced arterial disease of the major peripheral arteries and the distal aorta. In the present series, a diseased segment of a vessel has been replaced by a homograft in 264 patients, the majority of whom since have shown great clinical improvement. In nine patients in whom the homografts failed either during the immediately postoperative period or during the ensuing 18 months, the homografts were recovered for critical analysis at reoperation or at necropsy. The findings on these studies are presented in this report.

Materials and Methods

Nine homografts were available for study; five of these were recovered from 4 to 8 weeks and four from 9 to 18 months after the primary operation. Changes observed in the homografts in the early group were similar, and one was chosen for this report as representative for the preparation of photomicrographs and for comparison with the older segments.

All of the recovered homografts were processed in the same way. Blocks were taken from the central portion of the homografts and anastomotic lines, usually after fixation of the main portions of the specimen in Zenker's solution. The sections were stained with hematoxylin-eosin-methylene blue, Verhoeff's stain counterstained by the Van Gieson's method, Masson's trichrome stain, and Gomori's elastic tissue stain. Frozen sections were made on formalin-fixed segments and were stained with Sudan IV for lipids.

An unused freeze-dried femoral homograft was reconstituted as though for operative substitution and then was studied according to the procedures used for the collected material. The unused segment was essentially a fibroelastic tubular structure devoid of intima and lined by the internal elastic lamella (Fig. 1). There was a variable amount of adventitious tissue present. The media was composed of smooth muscle and fibrous tissue in the usual proportions.

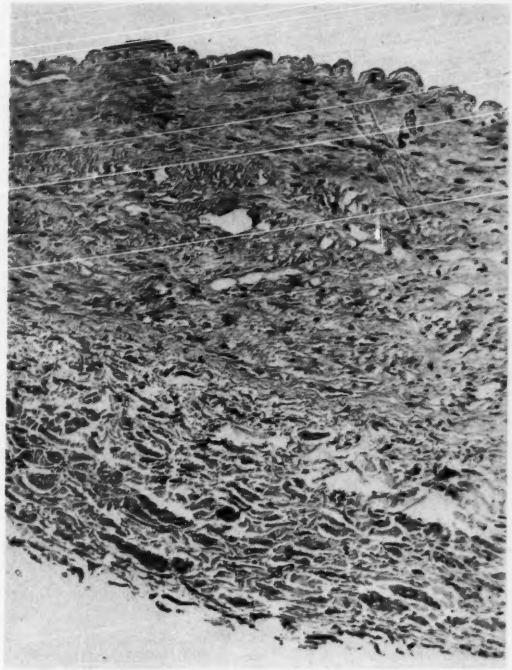

Fig. 1 (Unused, reconstituted, femoral homograft segment). Fibroelastic segment showing pyknotic smooth muscle nuclei. Hematoxylin-eosin-methylene blue; X95.

Nuclei of the smooth muscle were hyperchromatic, flattened, and fusiform; the nuclear detail was obscured. The adventitious zone was well defined and was of variable thickness because it had been stripped in processing. It consisted of interlacing collagen bundles, some of which appeared to be basophilic. The adventitious arterioles were well preserved; their smooth muscle cells appeared to be similar to those of the media. Sections stained with the Verhoeff's method showed many parallel and anastomosing elastic bundles in the media and few in the adventitia (Fig. 2). The internal elastic lamella was especially prominent and represented the inner surface of the homograft segment. Masson's trichrome stain revealed abundant collagen in the adventitia and media. Moreover, the Masson's stain clearly demonstrated vacuolated phagocytes in an old atheroma that in the hematoxylin-eosin-methylene blue preparations were observed as poorly outlined cells with unstained nuclei. No lipid was demonstrable in the vascular wall in sections prepared with Sudan IV.

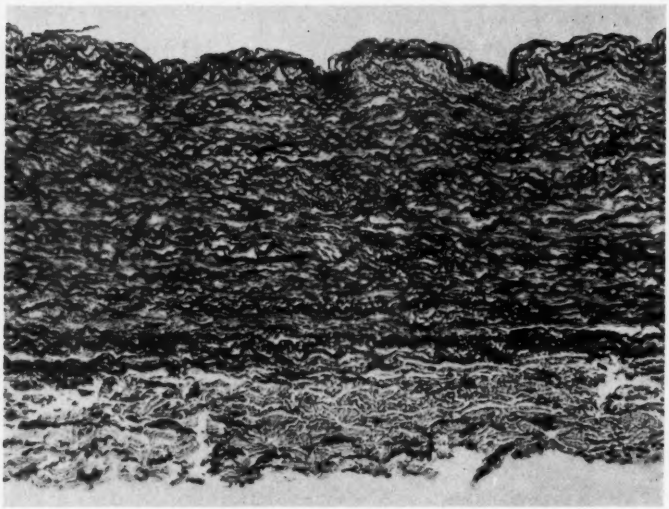

Fig. 2 (Unused, reconstituted, femoral homograft segment). Showing abundant elastic fibers in the media, and the internal elastic lamella as the lining surface. Verhoeff's stain; X140.

Case Reports

Case 1 (Eight-week graft). A diabetic, 56-year-old woman was admitted to the hospital because of intermittent claudication of the right calf after one block of normal walking; the condition had been present for one year without progression. In the right leg, there was a 2 plus femoral pulse with no pulsations below that level. Pulses in the left leg were essentially normal. The oscillometric measurements on the right were as follows: thigh ½ unit at 100 mm. Hg, below the knee ½, and above the ankle ½ unit. At operation a superficial femoral freeze-dried homograft was placed from the level of the bifurcation of the femoral artery to the popliteal space. The homograft was a primary failure. A second attempt at grafting was made two months later, at which time the first homograft was obtained for study. At the second operation, a segment of the right superficial femoral artery was replaced by a 14.5-cm. aortic homograft with end-to-end anastomoses.

The first aortic homograft was thickened, covered by dark-red, shaggy, fibrous tissue, and had the external diameter of a normal femoral artery. Because of technical difficulty, the homograft was removed in short segments. The lumen was completely occluded by a light-red thrombus that was adherent to the wall. The anastomotic lines were intact and the minute wedge-shaped depressions at these sites were filled with fibrin-like material. The intimal surface adjoining the clot was light ocher, smooth, and without intimal plaques, ulcerations, or focal zones of calcification. The proximal portion of the homograft had been plicated to reduce the size of the lumen, and five black-silk sutures were present.

Histologically, the graft appeared to be similar to the unused segment. The tunica intima was well defined but in all sections was devoid of any endothelial covering, and

appeared as a network of interlacing and occasionally nodulated fibers having a looser arrangement than those of the underlying tunica media. Elastic tissue stains showed moderately abundant elastic fibers, but these were not so dense as those in the underlying media. Masson's trichrome stain revealed only scant amounts of collagen in the tunica intima. This portion of the tunica intima corresponded to the internal elastic lamella of the muscular arteries. The elastic tissue content of the media appeared of normal amount; both the intima and the media were acellular at this eight-week stage.

About the periphery of the homograft there was an irregular but moderately thick cuff of granulation tissue that was heavily infiltrated by lymphocytes and plasma cells and showed a foreign-body reaction with many giant cells (Fig. 3). Numerous fibroblasts

Fig. 3 (Case 1—Eight-week-old homograft). Section showing dense foreign-body and inflammatory reaction in the adventitious zone. Hematoxylin-eosin-methylene blue; X30.

were present and they partially penetrated the superficial outer layers of the segment and formed fibrous tissue bundles with few or no elastic fibers. The inflammatory reaction was sharply delimited from the media, and the fibroblastic penetration apparently was limited to the scanty adventitia remaining on the vascular segment. Where the aortic segment had been plicated to reduce the size of the lumen, fibroblasts aggregated along the surgically cut surface and extended inward for a short distance parallel to the medial fibers (Fig. 4).

Case 2 (Nine-month graft). A nondiabetic, 53-year-old man was admitted to the hospital because of intermittent claudication of the left calf at two blocks of normal walking; it had been present for three months with no progression. The pulses were normal in the right leg. In the left leg, he had a 3 plus femoral pulse and no pulsations

Fig. 4 (Case 1—Eight-week-old homograft). Free margin of plicated homograft (upper right part of photograph) showing granulation tissue, marginal foreign-body reaction, and fibroblasts penetrating parallel to medial fibers. Hematoxylin-eosin-methylene blue; X80.

below that level. The oscillometric measurements in the right leg were normal; in the left leg they were as follows: thigh ¾ unit at 100 mm. Hg, below the knee ½, above the ankle ½ unit. On December 28, 1954, a superficial femoral artery was replaced with a freeze-dried, plicated, aortic homograft in Hunter's canal, resulting in full restitution of pulses. Nine months postoperatively he developed an acute aneurysm of the homograft with rupture. The ruptured homograft was successfully replaced and was obtained for study.

At reoperation a large aneurysmal dilatation of the femoral aortic homograft was found in Hunter's canal. The aneurysm measured 12.0 cm. in length and was flattened on its undersurface and protruded anteriorly in a rounded domelike fashion. It was surrounded by a large hematoma that was readily evacuated. The external surface was covered with abundant, thick, shaggy, densely adherent, fibrous tissue. Superiorly, a 4.5-cm. segment of the patient's vessel entered the aneurysm and the anastomotic site appeared to be well united and smooth. The patient's distal arterial segment was identified and the suture line at the anastomosis was found to be intact. On dissection the proximal arterial wall of the patient was 3.0 mm. in thickness and showed an extensive atheromatous process with numerous irregular yellowish raised plaques. The arterial segment was slightly constricted, where it anastomosed with the homograft. The aneurysm itself was filled with dark-red, extremely adherent, clotted blood, and yellowish pultaceous material.

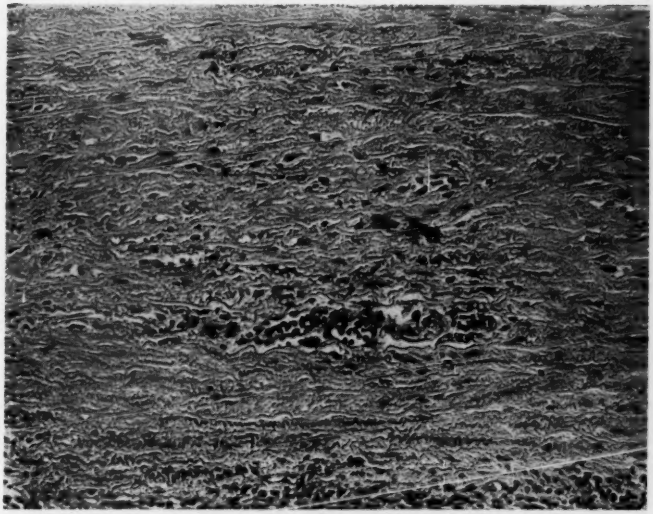

Fig. 5 (Case 2—Nine-month-old homograft). Blood-filled capillary in the outer portion of the media (lower part of photograph). Hematoxylin-eosin-methylene blue; X170.

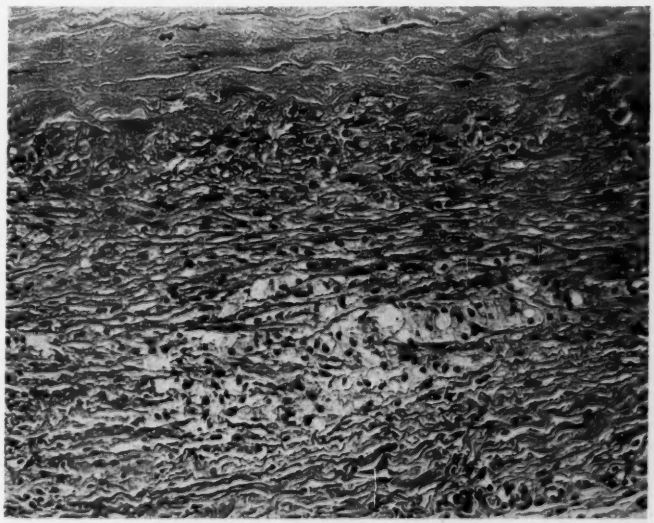

Fig. 6 (Case 2—Nine-month-old homograft). Collection of lipophages with scant lymphocytic infiltrate in the media. Hematoxylin-eosin-methylene blue; X170.

Traversing the length of the homograft was a continuous black-silk suture that had previously plicated the homograft to correct the size of the lumen. The wall of the aneurysm ranged from 0.5 to 1.0 cm. in thickness and was firm and rubbery; the distal opening was completely occluded by an atherosclerotic process.

In none of the histologic preparations could a lining endothelium be found in the aortic graft. The lumen of the aneurysm contained abundant old fibrin clot that was not organized but, in a few areas, the clot was invaded by fibroblasts. In many zones the inner two thirds of the media was acellular; the outer one third contained evenly distributed but sparse numbers of fibrocytes. An occasional blood-filled capillary was present in the outer portion of the media (Fig. 5). Numerous collections of lipophages were present, some just beneath the intimal tunic but most in the central and outer portions of the media (Fig. 6). In several sections, the media was thinned to approximately one half of its average thickness, and in one section a thin portion contained especially numerous foci of well-preserved lipophages. Verhoeff's stain showed abundant elastic tissue fibers in the relatively unaffected portions, but where the segment was thinned, the elastic fibers were condensed and sparse in number (Fig. 7). It appeared that the collections of lipophages produced the disruption in continuity of elastic tissue, maximally affecting the areas of greatest thinning. Masson's trichrome stain showed abundant collagen in the media in many areas, but the collagen fibers were spread apart and displaced by lipophage infiltration. In one thinned area, there was a pronounced reduction in collagen, particularly in the outer one half of the media. The adventitia of the homograft was comprised largely of dense collagen with a focal scanty lymphocytic infiltrate.

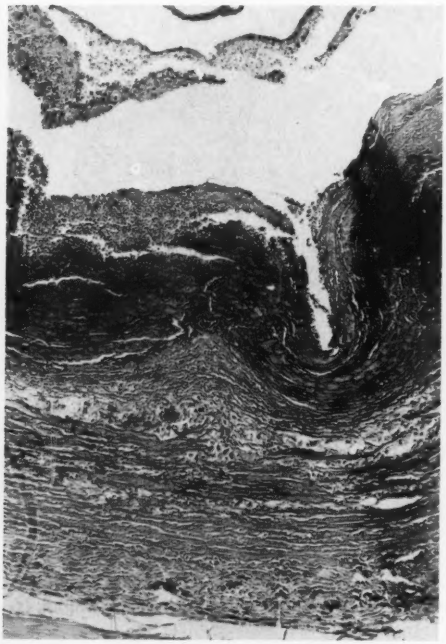

Fig. 7 (Case 2—Nine-month-old homograft). Section from aneurysmally dilated homograft showing sparse elastic fibers in broad outer zone of media, marked lipophage infiltration, and reduction in thickness of the media. Verhoeff's stain; X80.

Case 3 (Eleven-month graft). A nondiabetic, 59-year-old man was admitted to the hospital because of chest pain and intermittent claudication of the left buttock and left thigh which occurred after one-half block of normal walking; this condition had been present for six years and was becoming worse. The pulses on admission were as follows: right iliac 3 plus, right femoral 3 plus, right popliteal 3 plus, right dorsal pedal 0, right posterior tibial 2 plus. On the left side there were no pulsations below the aorta. Preoperative oscillometric measurements were as follows: on the right side—thigh ¾ unit at 100 mm. Hg, below the knee 2, above the ankle 1¾ units; on the left side—thigh ¼ unit at 100 mm. Hg, below the knee ½, above the ankle 0. A freeze-dried homograft was substituted for the aortic bifurcation including the left femoral bifurcation. Eleven months later the homograft suddenly ruptured because of erosion by sharp calcific points on the patient's left common iliac artery where it was cut at the time of the original homograft. An emergency operation was performed and another homograft was installed between the right common iliac portion of the original graft and the right femoral artery. The patient developed an infected retroperitoneal hematoma and died six days postoperatively.

At necropsy the thoracic and upper abdominal aorta showed severe arteriosclerosis. An infected hematoma extended from beneath the inguinal ligament on the left to the posterior portion of the pancreas and surrounded the psoas muscle, the sciatic nerve, the left kidney, and the adrenal. A recent aortic homograft segment, 20.0 cm. in length, was anastomosed to the right portion of the aortic bifurcation and to the right femoral artery distal to the femoral bifurcation. The proximal portion of the left homograft was ligated near the bifurcation. A 10-cm. segment of the old homograft extended from the region of the bifurcation down into the hematoma in the left inguinal region. Dissection of the vessels showed intact suture lines for the recent right femoral aortic homograft and a recently formed reddish-brown friable thrombus partially occluding the central portion of the old homograft. In several areas in the new segment there were yellowish, subintimal plaques of gritty consistence which were slightly elevated above the lining surface. The old homograft segment showed a roughened surface and had a tendency to separate into two layers. The distal portion was severely autolyzed and was lost in the hematoma; it was presumed to have sloughed off. The calcified segment of the left common iliac artery had been removed at the previous emergency operation.

Section of the 11-month-old homograft showed perivascular fibroblastic proliferation in an area that contained much hemosiderin pigment and notable infiltration with neutrophils, lymphocytes, and plasma cells. Numerous focal zones of autolysis were present. This autolytic process principally involved the adventitia, and the media singularly was spared and was present as an acellular necrotic segment without endothelial lining. Elastic tissue stains revealed abundant elastic fibers in parallel arrangement and in approximately the same amount as in a comparable unused aortic segment from the patient. Masson's trichrome stain reflected an amount of collagen similar to that in an unused aortic segment.

The recent homograft segment was identical to the unused segment except for the presence of old atheromas that were completely acellular but contained focal deposits of calcium. This segment was not included as part of this study.

Case 4 (One-year and one-and-one-half-year grafts). A nondiabetic, 47-year-old woman was admitted to the hospital because of claudication in the back and in both hips after three blocks of normal walking; the condition had been present for four years and was worsening. The preoperative pulses were normal on the right side; on the left side they were as follows: 2 plus femoral, 2 plus popliteal, and 2 plus posterior tibial. The preoperative oscillometric measurements were: on the right—below the knee 2½ units at

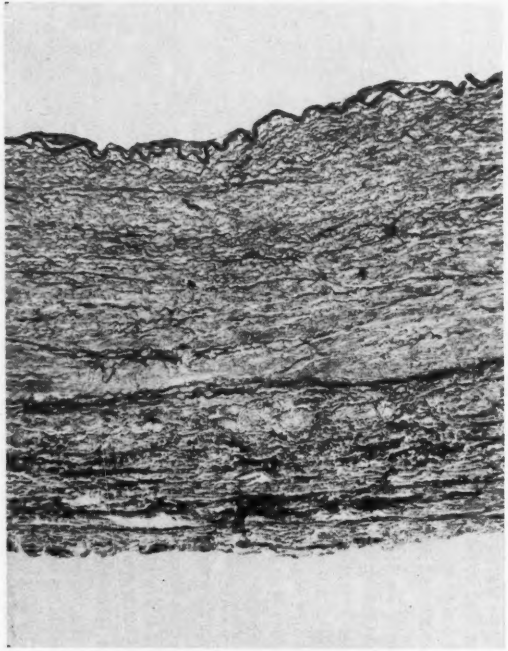

Fig. 8 (Case 4—One-year-old homograft). Showing the internal elastic lamella as the lining surface. Verhoeff's-Van Gieson's stains; X85.

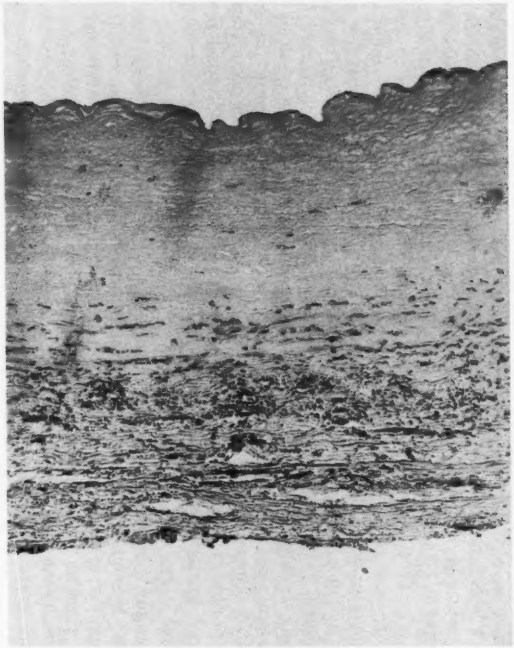

Fig. 9 (Case 4—One-year-old homograft). Extent of fibrous tissue infiltration of the media. The majority of the nucleated cells are fibrocytes. Hematoxylin-eosin-methylene blue; X80.

100 mm. Hg, above the ankle ¾ unit; on the left—below the knee ½, above the ankle ½ unit at 100 mm. Hg. A freeze-dried homograft was substituted for the aortic bifurcation, resulting in full restitution of normal pulses and oscillometric measurements. The patient remained well for seven months, when she again developed intermittent claudication. This condition was treated symptomatically. Six months later she was found to have a segmental occlusion of the left common iliac artery; the diseased segment of artery was removed and a bypass homograft connecting the right common iliac artery to the left common iliac artery was installed. Part of the first homograft was removed during that operation. Her condition remained unchanged for six months, by which time all pulses on the left lower extremity had disappeared. At a third operation, it was found that she had developed a secondary block at the femoral bifurcation with occlusion of the superficial femoral artery at that point. We believe that this represented diminution in exit flow which brought about an occlusion of the left half of the first homograft. The right side of the bifurcation had remained open. Accordingly, the bypass homograft was removed and a new prosthesis was substituted which included the femoral bifurcation.

At the second operation, one year after the initial grafting procedure, a segment of artery, 4.0 cm. in length and 0.5 cm. in diameter, was obtained. One end of the vessel showed an attached femoral graft of slightly larger caliber, the lumen of which was completely occluded. The artery itself was completely occluded 1.0 cm. from the site of the homograft. The anastomotic line appeared to be well healed and bound externally by dense collagen; the internal defect between the homograft and the patient's vessel was filled with fibrous tissue. Grossly, no intima appeared to cover the anastomosis.

Histologically, the patient's artery was occluded by an organizing thrombus; no endothelial lining could be discerned within the homograft. The defect between the donor segment and the patient's vessel was filled with fibrous tissue.

Multiple sections from the central portion of the graft showed essentially a tubular segment lined by the internal elastic lamella (Fig. 8). The inner portion of the media was acellular, but the outer one third to one half contained a few fibrocytes (Fig. 9). The distribution of the fibrocytes was sparse in many areas and more dense in others, particularly toward the adventitia. In focal areas, there was disruption of the media by a collection of irregular spaces, some of which contained the outlines of poorly preserved lipophages with foamy cytoplasm, but with no nuclei visible (Fig. 10). Masson's trichrome stain readily revealed these cells, stained the nuclei, and demonstrated the abundant collagen in the media and the adventitia. Verhoeff's stain showed the internal elastic lamella lining the vessel, but indicated a reduction in the content of elastic fibers in the media and the adventitia. Gomori's stain, however, revealed the elastic tissue fibers and they did not appear reduced in amount (Fig. 11). Sudan IV preparations showed that throughout the wall lipid droplets were focally dense, particularly beneath the internal elastic lamella.

The surgical specimen removed at the time of the third operation, one and one-half years after transplantation, was an aortic bifurcation homograft with the proximal aortic anastomotic line and an 0.8-cm. segment of the patient's aorta. A 2.0-cm. length of the right common iliac artery and a 3.5-cm. length of the left common iliac artery were part of the homograft. A 1.8-cm. length of femoral homograft was anastomosed end-to-side to the anterior portion of the right common iliac segment and was passed toward the left as part of the bypass. This was a portion of the one-year-old graft described above which had been ligated and left in the patient. The opened specimen showed complete thrombosis of the right iliac segment and of the more recent bypass. The left iliac portion showed considerable roughening of the lining surface by a focal mural thrombus. The aortic anastomosis was well united externally by dense fibrous tissue, and internally there

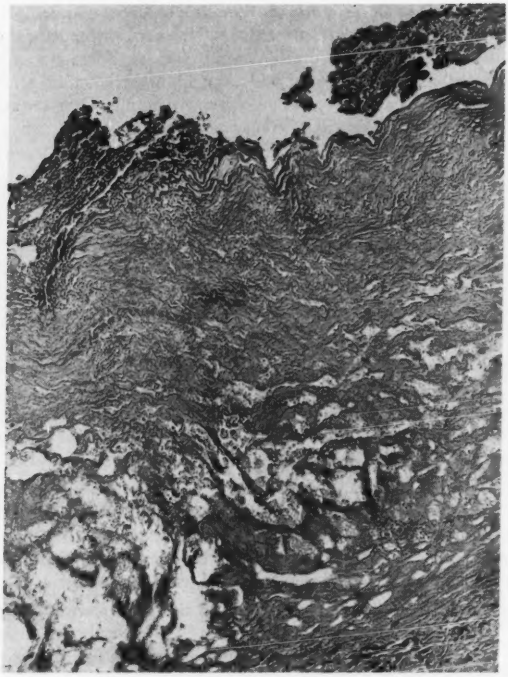

Fig. 10 (Case 4—One-year-old homograft). Section showing irregular atheromatous spaces in the media containing cells (lipophages) mostly with unstained nuclei; only a few pyknotic forms evident. Hematoxylin-eosin-methylene blue; X95.

was a slight wedge-shaped depression which appeared filled with fibrous tissue. The right iliac anastomosis was available as a second specimen and this showed a similar type of union. The left iliac anastomosis unfortunately could not be obtained.

Sections from the aortic anastomosis showed good union between the donor segment and the patient's vessel. Dense collagen filled the triangular defect at the junction of aorta and homograft, and a dense adventitia abundant in collagen also was present. No endothelium could be seen. The patient's own vessel showed numerous atheromas. Similar changes were noted at the other anastomoses and in none could endothelium be identified.

The central portions of the iliac homografts were not significantly different from the one-year-old segments. No evidence of endothelium was noted, and the internal elastic lamella lined the structure. The collagen and elastic tissue content of the media closely resembled that of the previously described one-year-old segment. The adventitia was present as an enveloping fibrous lamina of variable thickness, which contained focal lymphocytic infiltration and focal zones of fibroplasia. Sudan IV stains revealed lipid droplets in the vascular wall, which were focally aggregated particularly beneath the elastic lamella and in the adventitia.

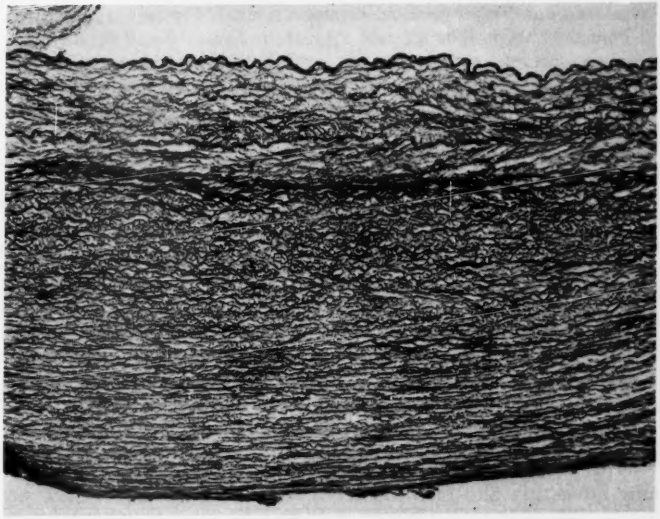

Fig. 11 (Case 4—One-and-one-half-year-old homograft). The Gomori elastic tissue stain shows the internal elastic lamella as the lining surface. There appears to be no significant reduction in elastic fiber content of the media. X95.

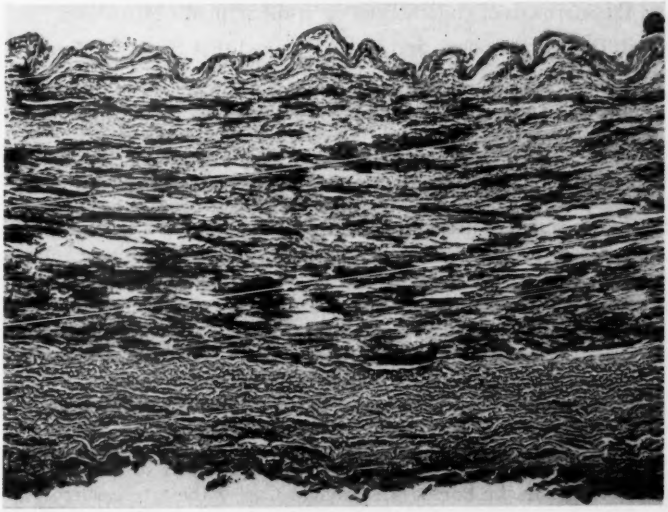

Fig. 12 (Case 4—One-year-old homograft). Showing fragmentation of the media and numerous irregular spaces. Masson's trichrome stain; X140.

The sections from the one-year-old bypass homograft showed no adventitious contribution from the patient. The internal elastic lamella was the lining membrane, but in small foci was covered by fibrin clot that distally occluded the lumen. The media had a peculiar appearance in the sections stained with hematoxylin-eosin-methylene blue, in that the fibromuscular tissue was fragmented and numerous irregular spaces were present (Fig. 12). The adventitia appeared as necrotic, irregularly interrupted bundles of collagen. The Masson's trichrome stain showed fragmentation of the collagen of the media and a marked diminution in collagen content. The tissue that failed to take the fast green stain appeared as short, rectangular, fragmented, coarse fibers. Verhoeff's stain showed an intact internal elastic lamella and a marked reduction in elastic tissue in the media, but well-retained elastic tissue in the adventitia. The elastic fibers that remained in the media appeared condensed and, in most foci, were discontinuous and of short, irregular contour.

Comment

From the study of the present series the fate of homograft segments appears to be as follows. In part they become "vitalized" by fibrocytic infiltration of the remaining adventitia and of the outer layers of the media. From a practical point of view, the patient actually contributes a new adventitia that is moderately vascular; indeed, a few capillaries can be found in the outer layers of the media where there has been fibrous tissue infiltration. The elastic tissue of the media appears to be well retained. The internal elastic lamella or its equivalent in the aorta serves as the lining surface, and in none of our sections have we observed the ingrowth of endothelium from the patient's own vessel.

Creech, DeBakey, Cooley, and Halpert[1] noted that the intimal surface near the anastomotic line becomes covered by endothelium and the central portions by an amorphous fibrinoid substance. Barberio, Pate, Sawyer, and Hufnagel[2] also reported this endothelialization as occurring experimentally in animals, but they used only fresh aortic homografts. There is no doubt that such endothelial ingrowth does occur and a possible reason that we have not observed it, is that in all of the cases presented, thrombosis with occlusion of the homograft has been present. This cessation of blood flow probably suppresses proper nutrition to the intima and causes the disintegration of the endothelial ingrowth over the anastomoses.

Homografts are prone to develop arteriosclerosis, and this is logical since, as Creech and his group[1] point out, the homograft is subjected to the same internal environment as the patient's own vessels. Fisher and Fisher[3] were able to produce arteriosclerotic changes in homografts in experimental animals. Creech and associates[4] observed that when serum cholesterol levels in dogs were maintained at 1000 mg. per 100 ml., both the homograft and the dog's aorta developed atheromatous changes, and that lower levels of serum cholesterol produced changes in the homograft only. In Case 2 the arteriosclerotic process was manifested by numerous collections of lipophages within the media but without deposits of free cholesterol. These collections of lipophages disrupted the

continuity of the medial elastic fibers and collagen bundles, and in some areas appeared to occupy a considerable portion of the media. Infiltration by lipophages was most noticeable in those zones associated with the greatest thinning of the media. The aneurysmal dilatation of the homograft apparently is related to the infiltration by lipophages.

The durability of homograft segments would seem to be excellent. With one exception (Case 2), we have observed no failure of a homograft because of structural changes within the homograft itself. Probably this durability is due to the preservation of the elastic tissue component and to the presence of adventitia supplied by the patient. In some cases the elastic tissue undergoes alteration in staining reaction and Verhoeff's stain fails to reveal all of the elastic fibers that are readily visible by the Gomori method. There was no significant diminution of elastic fiber content in the one-year-old and in the one-and-one-half-year-old specimens. The collagen of the media was similarly well retained. This retention of structural integrity supports the view that homografts are good for many years and the experience of others is in close agreement.[1]

The peculiar changes observed in the one-year-old bypass homograft segment in Case 4 were not seen in any of our other material. The fragmentation of the media with condensation and reduction in elastic fiber content and diminution of collagen were interpreted as changes relating to nonfunction. This bypass segment was present in the patient for one year and was ligated at its distal end. The patient had not contributed a new adventitia as evidenced by the acellular and necrotic appearance of the adventitious zone. Evidently this homograft segment acted as a nonirritating foreign body and slowly underwent the degenerative changes observed.

Summary

Arterial freeze-dried homografts are essentially fibroelastic tubular "prostheses" of considerable durability. At least in the central portions of the homografts the lining surface appears to be the internal elastic lamella or its equivalent. The elastic tissue content of the media of homografts is well retained after one and one-half years though it undergoes changes indicated by altered staining properties. To a great extent the adventitia is supplied by the patient and, in some homografts, fibrous connective tissue may infiltrate the outer layers of the media. Endothelialization was not observed, and this lack in these cases might be the result of thrombosis within and near the homograft. Arteriosclerosis may develop in the media of homografts and in one case was sufficiently severe to permit formation of an aneurysm.

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ANGIOGRAPHY OF THE CORONARY ARTERIES IN THE LIVE DOG

II. Detection of Abnormalities

EDWARD W. MILLER, M.D.,*
Division of Research

C. ROBERT HUGHES, M.D.,
Department of Radiology

and

WILLEM J. KOLFF, M.D.
Division of Research

AN earlier article[1] reported our experience with coronary angiography in normal dogs. The present report describes observations on the angiographic diagnosis of experimentally induced abnormalities of the coronary arteries in dogs.

Procedure

The procedure used was described in the previous article[1] and need not be reported in detail. Mongrel dogs were used, weighing approximately 10 kg. each. Angiograms were made under morphine-pentobarbital (Nembutal sodium, Abbott) anesthesia. A 50-cm. cardiac catheter was passed into the root of the aorta through a carotid artery if available, but brachial and femoral arteries were employed with equal success. We depended on our sense of touch and fluoroscopy to place the catheter tip near the coronary ostia.

Injections of radiopaque medium were made either rapidly or slowly. Ninety per cent Hypaque sodium (sodium diacetrizoate, Winthrop) was used as the contrast medium in seven, and 70 per cent Diodrast (iodopyracet, Winthrop) in six experiments. The contrast medium usually was injected in 10-cc. amounts at intervals of a few minutes. The average total dose of Hypaque sodium was 43 cc. per dog, or approximately 4 cc. per kilogram of body weight; one dog received 86 cc. within one hour's time. The average total dose of Diodrast was 55 cc. per dog, or about 5.5 cc. per kilogram; one dog received 80 cc. within one hour's time.

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**Special Fellow, Division of Research.*

Eleven dogs survived the coronary artery defects that had been produced days or months before in the following ways: (1) ligation of major coronary artery, three dogs; (2) ligation of branches of a major coronary artery, three dogs; (3) narrowing of a major coronary artery at one point by tying a silk ligature over a No. 20F needle and then withdrawing the needle, three dogs; and (4) complete division and reanastomosis of a major coronary artery during induced cardiac arrest while the systemic circulation was maintained by a heart-lung machine, two dogs.

Results

Effects of injecting contrast medium. Immediately after receiving an injection of contrast medium, most dogs exhibited a brief period of apnea followed by hyperpnea and transient tachycardia. There were no other ill effects apparent when 90 per cent Hypaque sodium was used.

Reactions to Diodrast were more pronounced. This was anticipated, and Diodrast was used only when our supply of Hypaque sodium was exhausted. After Diodrast, occasionally there were signs of central nervous irritation with extensor movements and evacuation of the rectum. Tonic movements of the body could be elicited by sudden noise or by moving the operating table. One dog that

Fig. 1 (Ligation of right coronary artery). Only the stump of the right coronary artery is filled; the branches of the left coronary artery are clearly visible.

Fig. 2 (Ligation of anterior descending branch of left coronary artery). **A**, Since the tip of the catheter is in the right sinus, the right coronary artery is filled best, but contrast medium spills over into the left sinus of Valsalva. The anterior descending branch of the left coronary artery is not seen, but the left circumflex and septal branches are well filled. **B**, Diagram to show the anatomic relationship of the vessels seen in **A**. The stump of the anterior descending branch of the left coronary artery cannot be seen in the angiogram and has been sketched in to show its anatomic position. The right coronary artery, RC; the septal branch, S; and the left circumflex branch, LC.

Fig. 3 (Narrowing of anterior descending branch of left coronary artery). The tip of the catheter is in the left sinus of Valsalva so that the left coronary artery is filled. A narrow area in the anterior descending branch of the left coronary artery is indicated by the arrow. Above the narrowing, the septal artery is filled. The right coronary artery is not seen in this roentgenogram but was visualized on others.

Fig. 4 (Narrowing of circumflex branch of left coronary artery). The defect is indicated by the arrow. All three coronary arteries are filled.

Fig. 5 (Narrowing of anterior descending branch of left coronary artery). In these two roentgenograms the effects of a slight rotation in the position of the dog are noted. **A**, The narrow area in the anterior descending branch of the left coronary artery is hidden by the septal branch in the oblique view, but it is brought into relief, **B**, when the dog's position was rotated laterally.

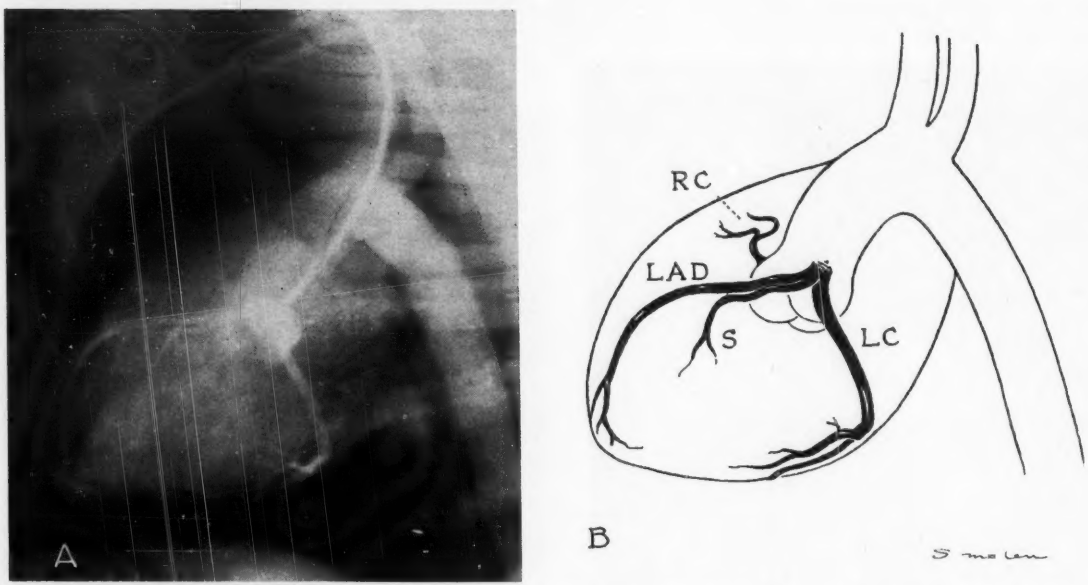
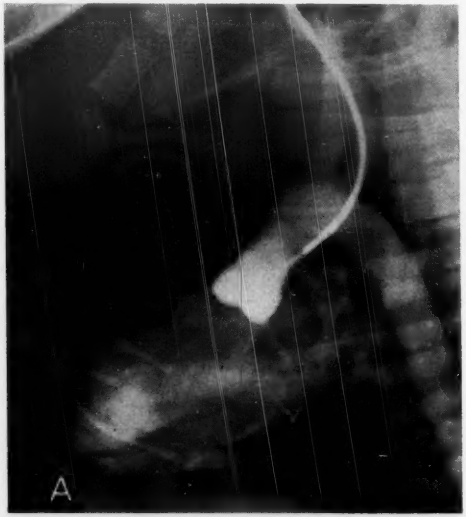


Fig. 6 (Division and reanastomosis of anterior descending branch of left coronary artery). **A**, The tip of the catheter is in the left sinus of Valsalva. The left coronary artery is filled. The left anterior descending branch is well filled and without evidence of defect. The point of anastomosis cannot be seen. **B**, Diagram of **A** to show anatomic relationship of the vessels.



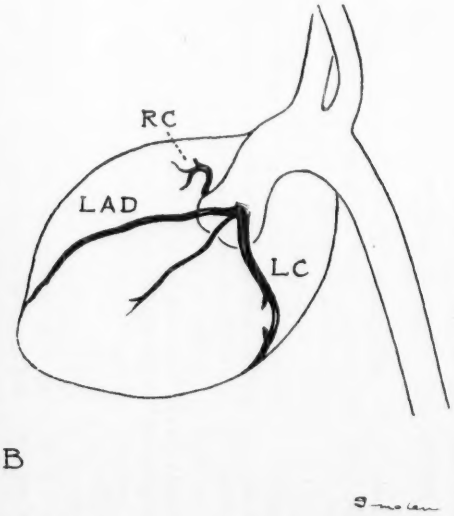


Fig. 7 (Division and reanastomosis of right coronary artery). **A**, Filling of the coronary system is not good since the catheter is too far from the base of the aorta. Despite this poor filling, the right coronary artery can be seen to be functioning. The area of anastomosis is not noticeable. **B**, Diagram of **A**, to show anatomic relationship of the vessels.

received 80 cc. of Diodrast within one hour's time, died the night after angiography. This animal had had ligation of the right coronary artery two months prior to the studies. The cause of death could not be determined at autopsy.

In another dog that had had division and reanastomosis of a major coronary artery and that was studied twice, a total of 20 cc. of Hypaque sodium was well tolerated; but one month later, 40 cc. of Diodrast produced a generalized convulsion.

Quality of angiogram. In each animal all three coronary arteries, when patent, filled satisfactorily with contrast medium. The three coronary arteries were best outlined when the animal was in the lateral or in the left posterior oblique position. The position of the catheter was of importance in obtaining satisfactory visualization. Since there are three sinuses of Valsalva, right, left, and posterior, and coronary arteries arise only from the right and the left, it is best to place the catheter tip near the ostium of the artery that one wishes to fill. With rapid injection there is overflow of the contrast medium into adjacent sinuses; with slow injection this overflow is less likely to occur.

Accuracy of angiographic interpretation. In the three dogs that had ligation of one of the main coronary arteries, the involved vessels were easily recognized by their failure to fill (Figs. 1 and 2).

In the three dogs that had ligation of one or more branches of the left coronary artery, it was not possible to determine roentgenographically which branches were tied off. The wide range of normal variation in the structure of the coronary arterial tree made it impossible to identify a vessel as missing.

In the three dogs with narrowing of a major artery, the roentgenograms clearly demonstrated the areas so treated (Figs. 3 and 4). Rotation of the dog's position in either direction from the lateral brought into relief the origin of the artery from the sinus of Valsalva as well as the first centimeter of the artery. In the oblique view the septal artery might override the anterior descending artery, obscuring the first third of the latter vessel (Fig. 5A). Rotation to the lateral obviated this source of error (Fig. 5B).

In the two dogs in which coronary arteries had been divided and reanastomosed (Figs. 6 and 7), the vessels were filled with contrast medium, showing their patency. The area of suture could not be identified, probably because of the absence of narrowing at the suture line.

Summary

Angiography was found to be a dependable procedure in localizing sites of partial or complete occlusion of any of the main coronary arteries in 10 experiments in living dogs. Occlusion of side branches of the main arteries could not be detected by this means. Ninety per cent Hypaque sodium proved to be a safe contrast medium for this purpose.

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**Formerly Special Fellow in the Department of Endocrinology.*

***Fellow in the Department of Neurosurgery; on leave of absence.*

†*Fellow in the Department of Anesthesiology.*

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**Formerly Fellow in the Department of Endocrinology.*

***Formerly Fellow in the Department of Clinical Pathology.*

†Senior Instructor in Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

††Head of the Department of Biology, Fenn College, Cleveland, Ohio.

§Hektoen Institute for Medical Research of Cook County Hospital, Chicago, Illinois.

§§Work done while Doctor Scherbel was with United States Naval Hospital and Naval Medical Research Unit No. 4, Great Lakes, Illinois.

#United States Naval Medical Research Unit No. 4, USNTC, Great Lakes, Illinois.

##Fellow in the Division of Medicine.

//Formerly Fellow in the Division of Research.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

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THE CLEVELAND CLINIC FOUNDATION

announces a postgraduate continuation course in general practice on February 6 and 7, 1957
sponsored by the
Cleveland Chapter of the American Academy of General Practice

Tentative Program

Wednesday, February 6, 1957

Morning Session

8:00- 8:55	.	Registration
8:55- 9:00	.	Welcome, Introductory Remarks . . . . . CHARLES L. LEEDHAM, M.D. HERBERT W. SALTER, M.D.*
9:00-10:30	.	Panel Discussion: Psychiatric Medicine The Anxious Patient . . . . . RICHARD M. NELSON, M.D. The Timid Patient . . . . . GUY H. WILLIAMS, JR., M.D. The Agitated Senile Patient . . . . . LOUIS J. KARNOSH, M.D. The Function of Tranquilizers . . . . . LEONARD L. LOVSHIN, M.D.
10:30-10:50	.	Intermission
10:50-11:10	.	Facets of Pediatric Diagnosis . . . . . ROBERT D. MERCER, M.D.
11:10-11:30	.	Hearing Problems in Children . . . . . WARREN H. GARDNER, PH.D.
11:30-11:50	.	Obstetrical Management of Abnormal Presentations . . . . . HOWARD P. TAYLOR, M.D.
11:50-12:10	.	Detection Methods in Pelvic Cancer . . . . . JAMES S. KRIEGER, M.D.
12:10-12:30	.	The Treatment of Sinus Diseases . . . . . CARL W. HOCH, M.D.
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session

1:30- 3:00	.	Panel Discussion: Hypertension Basic Hemodynamics . . . . . CARL J. WIGGERS, M.D. Hypertension: The Year in Research . . . HARRIET P. DUSTAN, M.D. Some Clinical Aspects of Hypertension . . DAVID C. HUMPHREY, M.D. The Management of the Hemiplegic Patient . . PAUL A. NELSON, M.D.
3:00- 3:30	.	Intermission
3:30- 5:00	.	Panel Discussion: Open-Heart Surgery The Artificial Heart . . . . . WILLEM J. KOLFF, M.D. Diagnosis of Surgically Correctible Heart Defects . . . . . F. MASON SONES, JR., M.D. Open-Heart Surgery . . . . . DONALD B. EFFLER, M.D.

*Chairman, Education Committee, Cleveland Chapter of the American Academy of General Practice.

Thursday, February 7, 1957

Morning Session

8:30-10:30 . Panel Discussion: Medicine

The Painful Leg . . . . . ALFRED W. HUMPHRIES, M.D.

Progress in the Management of Rheumatoid Arthritis . . . . . ARTHUR L. SCHERBEL, M.D.

Some Aspects of the Problem of Fever of Unknown Origin . . . . . RAY A. VAN OMMEN, M.D.

Treatment of Some Common Skin Diseases . . GEORGE H. CURTIS, M.D.

10:30-11:00 . Intermission

11:00- 1:00 . Panel Discussion: Surgery

Reversible Hypertension . . . . . EUGENE F. POUTASSE, M.D.

The Acute Abdomen . . . . . GEORGE CRILE, JR., M.D.

Care of Colostomies . . . . . RUPERT B. TURNBULL, JR., M.D.

The Orderly Approach to the Injured Individual . . . . . ROBIN ANDERSON, M.D.

2:00 . Tour of the Cleveland Clinic and of the Cleveland Clinic Hospital

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

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THE CLEVELAND CLINIC FOUNDATION

announces a postgraduate continuation course in otology, rhinology, laryngology, maxillofacial surgery, bronchoscopy, and esophagoscopy on February 27 and 28, 1957

Tentative Program

Wednesday, February 27, 1957

Morning Session . . . . . HAROLD E. HARRIS, M.D., *Presiding*

8:00- 8:55	.	Registration
8:55- 9:00	.	Welcome, Introductory Remarks . . . . . CHARLES L. LEEDHAM, M.D.
9:00- 9:20	.	Present-Day Concepts of Anesthesia in Head and Neck Surgery . . . . . DONALD E. HALE, M.D.
9:20- 9:40	.	The Diagnosis and Treatment of Sinus Diseases . . CARL W. HOCH, M.D.
9:40-10:00	.	Unusual Neoplasms of Head and Neck . LAWRENCE J. MCCORMACK, M.D.
10:00-10:45	.	Stapes Mobilization . . . . . HOWARD P. HOUSE, M.D.*
10:45-11:05	.	Intermission
11:05-11:25	.	Control of Hemorrhage in Otolaryngology . . FRED R. TINGWALD, M.D.
11:25-11:45	.	When Should a Hearing Aid be Recommended? . . . . . .WARREN H. GARDNER, PH.D.
11:45-12:30	.	Panel Discussion: Dizziness *Moderator*—HAROLD E. HARRIS, M.D. HOWARD P. HOUSE, M.D.* CHARLES E. KINNEY, M.D.* WILLARD PARKER, M.D.
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session . . . . . HAROLD E. HARRIS, M.D., *Presiding*

2:00- 2:45	.	The Noncommunicative Child—Age 1 to 6 Years. CHARLES E. KINNEY, M.D.*
2:45- 3:05	.	Vocal Cord Paresis and Paralysis . . . . . HAROLD E. HARRIS, M.D.
3:05- 3:25	.	Tracheotomy: Indications and Management . . WILLARD PARKER, M.D.
3:25- 3:45	.	Intermission
3:45- 4:30	.	Treatment of Acute and Chronic Otitis Media . . . . . HOWARD P. HOUSE, M.D.*
4:30- 4:50	.	Voice Problems . . . . . WARREN H. GARDNER, PH.D.
4:50- 5:30	.	Questions and Answers

*Guest speaker.

Thursday, February 28, 1957

Morning Session . . . . . HAROLD E. HARRIS, M.D., *Presiding*

9:00- 9:45	.	Congenital Anomalies of the Larynx . . . KENNETH C. JOHNSTON, M.D.*
9:45-10:05	.	The Radical Neck Operation: Indications and Technic . . . . . ROBIN ANDERSON, M.D.
10:05-10:45	.	Cancer of the Larynx and Adnexa . . . . . JULIUS W. MCCALL, M.D.*
10:45-11:00	.	Intermission
11:00-11:20	.	Cobalt-60 Teletherapy in Palliative Therapy for Cancer . . . . . ROBERT A. HAYS, M.D.
11:20-12:00	.	Panel Discussion: Malignancy of Head and Neck *Moderator*—HAROLD E. HARRIS, M.D. ROBIN ANDERSON, M.D. ROBERT A. HAYS, M.D. JULIUS W. MCCALL, M.D.* LAWRENCE J. MCCORMACK, M.D.
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session . . . . . HAROLD E. HARRIS, M.D., *Presiding*

2:00- 2:20	.	The Allergic Child . . . . . ROBERT D. MERCER, M.D.
2:20- 2:40	.	The Deviated Nose . . . . . FRED R. TINGWALD, M.D.
2:40- 3:30	.	Diagnosis and Management of Esophageal Disease in Children . . . . . KENNETH C. JOHNSTON, M.D.*
3:30- 3:50	.	Intermission
3:50- 4:10	.	Headache . . . . . LEONARD L. LOVSHIN, M.D.
4:10- 4:30	.	Chronic Cough . . . . . HOWARD S. VAN ORDSTRAND, M.D.
4:30- 5:00	.	Panel Discussion: Dyspnea in Infants and Children *Moderator*—ROBERT D. MERCER, M.D. KENNETH C. JOHNSTON, M.D.* FRED R. TINGWALD, M.D. HOWARD S. VAN ORDSTRAND, M.D.

Affiliations of Guest Speakers

HOWARD P. HOUSE, M.D., Professor of Surgery and Head of the Department of Otolaryngology, University of Southern California School of Medicine, Los Angeles, California.

KENNETH C. JOHNSTON, M.D., Assistant Professor of Broncho-Esophagology, University of Illinois College of Medicine, Chicago, Illinois.

CHARLES E. KINNEY, M.D., Otologist to Public and Parochial Schools, Cleveland, Ohio.

JULIUS W. McCALL, M.D., Surgeon, St. Luke's Hospital, Cleveland, Ohio.

**Guest speaker.*

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Medical Progress and Its Relationship to Dentistry

sponsored by

Cleveland Dental Society

Tentative Program

Wednesday, March 13, 1957

Morning Session . . . . . CHARLES A. RESCH, D.D.S., *Presiding*

8:15- 9:00	.	Registration
9:00- 9:10	.	Welcome, Introductory Remarks . . . . . CHARLES L. LEEDHAM, M.D., and E. CARL MILLER, D.D.S.*
9:10- 9:30	.	The Relationship of Ocular Manifestations to Dental Infection . . . . . ROSCOE J. KENNEDY, M.D.
9:30- 9:50	.	Surgical Management of Diseases of the Superior Maxilla . . . . . HAROLD E. HARRIS, M.D.
9:50-10:30	.	Progress in Oral Pathology and Its Relationship to Medicine . . . . . PAUL E. BOYLE, D.M.D.*
10:30-11:00	.	Intermission
11:00-11:20	.	The Dentist's Own Problem: The Prostate . CHARLES C. HIGGINS, M.D.
11:20-11:40	.	The Dentist's Own Problem: Hemorrhoids . . STANLEY O. HOERR, M.D.
11:40-12:00	.	The Dentist's Own Problem: Obesity . . . . . PENN G. SKILLERN, M.D.
12:00-12:15	.	Question and Answers
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session . . . . . E. CARL MILLER, D.D.S.,* *Presiding*

2:00- 2:20	.	The V lue of Hypnosis . . . . . HOWARD P. TAYLOR, M.D.
2:20- 2:40	.	Central Mechanisms in Oral Physiology . . . . LOUIS J. KARNOSH, M.D.
2:40- 3:30	.	Oral Pathology and Its Relationship to Tobacco Smoke . . . . . SEYMOUR KRESCHOVER, D.D.S.*
3:30- 4:00	.	Intermission
4:00- 4:20	.	Dermatological Lesions of the Face . . . . EARL W. NETHERTON, M.D.
4:20- 4:40	.	Renal Physiology . . . . . CARL J. WIGGERS, M.D.
4:40- 5:10	.	The Year in Dental Research . . . . . THOMAS J. HILL, D.D.S.*
5:10- 5:30	.	Questions and Answers

*Guest speaker.

Thursday, March 14, 1957

Morning Session . . . . . JOHN K. DUNN, D.D.S., *Presiding*

9:00- 9:20 . The Use of Tranquilizing Drugs . . . . . LEONARD L. LOVSHIN, M.D.

9:20- 9:40 . The Present Status of Antibiotics . . . . . RAY A. VAN OMMEN, M.D.

9:40-10:00 . The Aftereffects of Cortisone and Its Relationship to Oral Treatment . . . . . ARTHUR L. SCHERBEL, M.D.

10:00-10:20 . Medical Measures in Cardiac Emergencies . WILLIAM L. PROUDFIT, M.D.

10:20-10:40 . Current Progress in the Management of Hypertension . . . . . IRVINE H. PAGE, M.D.

10:40-11:10 . Intermission

11:10-11:30 . The Present Status of the Cancer Problem . . GEORGE CRILE, JR., M.D.

11:30 . Panel on Surgery

Moderator—THOMAS J. HILL, D.D.S.*
GEORGE CRILE, JR., M.D.
DONALD B. EFFLER, M.D.
ALFRED W. HUMPHRIES, M.D.
CHARLES A. RESCH, D.D.S.

Afternoon Session

1:30 . Tour of the Cleveland Clinic and the Cleveland Clinic Hospital

Affiliations of Guest Speakers

PAUL E. BOYLE, D.M.D., Dean, Western Reserve University School of Dentistry, Cleveland, Ohio. (Formerly Professor of Oral Histology and Pathology, School of Dentistry, University of Pennsylvania, Philadelphia, Pennsylvania.)

THOMAS J. HILL, D.D.S., Professor Emeritus, Western Reserve University School of Dentistry, Cleveland, Ohio.

SEYMOUR KRESCHOVER, D.D.S., Associate Director, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland.

E. CARL MILLER, D.D.S., President, Cleveland Dental Society, Cleveland, Ohio.

Registration Form on page 58.

*Guest speaker.

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(City and State) . . . . . .

Dental School . . . . . .

Date of Graduation . . . . . .

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announces a postgraduate continuation course in obstetrics and gynecology on March 21 and 22, 1957

Tentative Program

Thursday, March 21, 1957

Advances in Obstetric Care

Morning Session . . . . . HOWARD P. TAYLOR, M.D., *Presiding*

8:15- 8:55	.	Registration
8:55- 9:00	.	Welcome . . . . . CHARLES L. LEEDHAM, M.D.
9:00- 9:20	.	Recognition and Care of the Nervous Patient . . . . . LEONARD L. LOVSHIN, M.D.
9:20- 9:40	.	Emotional Aspects in Prenatal Care . . . . LEONARD H. BISKIND, M.D. *
9:40-10:00	.	Support During Labor . . . . . PAUL R. ZEIT, M.D.
10:00-10:20	.	Pediatric Aspects in Preparation for Parenthood . MARY HARMON, M.D.
10:20-10:40	.	Medical Responsibilities in Preparation for Family Living . . . . . ALBERT C. LAMMERT, M.D.
10:40-11:20	.	Intermission
11:20-11:40	.	A Nurse Looks at a Training Program for Childbirth . . . . . JEAN YEIGH, R.N.
11:40-12:00	.	A Doctor Looks at the Results of a Training Program for Childbirth . . . . . MARION E. BLACK, M.D. *
12:00-12:20	.	A Parent Looks at a Training Program for Childbirth . . . . . REV. PETER H. SAMSOM, D.D. *
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session . . . . . ALBERT C. LAMMERT, M.D., *Presiding*

1:30- 2:30	.	Psychophysiology of Normal Obstetrics . . . WILLIAM S. KROGER, M.D. *
2:30- 3:00	.	Intermission
3:00- 4:00	.	Round Table: Organization and Conduct of a Prenatal Training Program *Moderator*—WILLIAM S. KROGER, M.D. * LEONARD H. BISKIND, M.D. * MARION E. BLACK, M.D. * HOWARD P. TAYLOR, M.D.
4:00	.	Tour of Department of Obstetrics

*Guest speaker.

Friday, March 22, 1957

Gynecologic Bleeding

Morning Session . . . . . JAMES S. KRIEGER, M.D., *Presiding*

9:00- 9:20	.	Diagnosis and Treatment of Vaginitis . . . ALBERT C. LAMMERT, M.D.
9:20- 9:40	.	Lesions of the Vulva . . . . . JOHN R. HASERICK, M.D.
9:40-10:00	.	Benign Cervical Lesions . . . . . PAUL R. ZEIT, M.D.
10:00-10:20	.	Bleeding Associated with Early Pregnancy Complications . . . . . HOWARD P. TAYLOR, M.D.
10:20-10:40	.	Benign Uterine Lesions . . . . . ROBERT L. FAULKNER, M.D.*
10:40-11:00	.	Intermission
11:00-11:30	.	Menopausal and Postmenopausal Bleeding . . NORMAN F. MILLER, M.D.*
11:30-11:50	.	Adolescent Bleeding Problems . . . . . E. PERRY MCCULLAGH, M.D.
11:50-12:10	.	Clinicopathologic Correlation of Dysfunctional Bleeding . . . . . IRVING ROTHCHILD, M.D.*
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session

1:30- 3:00 . Panel Discussion: Carcinoma of the Cervix

Moderator—PAUL R. ZEIT, M.D.

Detection Methods—LAWRENCE J. MCCORMACK, M.D.

Irradiation Therapy—ROBERT A. HAYS, M.D.

The Place of Surgery—JAMES S. KRIEGER, M.D.

Care of the Hopeless Malignancy—NORMAN F. MILLER, M.D.*

Affiliations of Guest Speakers

LEONARD H. BISKIND, M.D., Chief of Obstetrics and Gynecology, Mt. Sinai Hospital, Cleveland, Ohio.

MARION E. BLACK, M.D., Assistant Clinical Professor of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, Ohio.

ROBERT L. FAULKNER, M.D., Associate Professor of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, Ohio.

WILLIAM S. KROGER, M.D., Clinical Associate Professor of Gynecology, Chicago Medical School, Chicago, Illinois.

NORMAN F. MILLER, M.D., Professor of Obstetrics and Gynecology, and Bates Professor of Diseases of Women and Children, University of Michigan Medical School, Ann Arbor, Michigan.

IRVING ROTHCHILD, M.D., Associate Professor of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, Ohio.

THE REV. PETER H. SAMSOM, D.D., Minister of West Shore Unitarian Church, Cleveland, Ohio.

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*Guest speaker.

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Please register me for the postgraduate continuation course in *Obstetrics and Gynecology*, to be given March 21 and 22, 1957. (*Registration fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.*)

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Name . . . . . .

Address (Street) . . . . . .

(City and State) . . . . . .

Name of Medical School . . . . . .

Date of Graduation . . . . . .

Present Practice is:
Full-Time Specialty . . . . . .

General Practice and Part-Time Specialty . . . . . .

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Pathology and Pathologic Physiology in Internal Medicine

The course will place emphasis on pathologic anatomy and current concepts of pathologic physiology in systemic disease. The principal objective will be to stress the relationship between pathology, pathologic physiology, and clinical diagnosis and treatment. The major subjects to be presented will be in the fields of cardiovascular and renal disease, pulmonary disease, gastroenterology, hematology, endocrinology, and metabolic disease. The course will include lectures, clinical demonstrations, pathology conferences, and question-and-answer panels.

Tuition will be $30.00 for members of the American College of Physicians and $60.00 for nonmembers. Application for registration in the course should be made directly to Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

The course will be given at the Cleveland Clinic which is located at Euclid Avenue and East 93 Street, Cleveland 6, Ohio. Nearby hotels having comfortable accommodations include the Wade Park Manor, Park Lane Villa, and Alcazar Hotel. Room reservations may be made now.

Tentative Program

Monday, March 25, 1957

Morning Session

8:00- 8:50	.	Registration
8:50- 9:00	.	Orientation . . . . . A. CARLTON ERNSTENE, M.D.
		Endocrinology and Metabolic Diseases
9:00-10:00	.	Pathology Conference: Pancreas, Adrenals, and Pituitary Gland . . . . . JOHN B. HAZARD, M.D. LAWRENCE J. MCCORMACK, M.D. E. PERRY MCCULLAGH, M.D. PENN G. SKILLERN, M.D.
10:00-10:15	.	Intermission
10:15-11:00	.	Clinical Aspects of Disturbed Pituitary Function . . . . . WILLIAM MCK. JEFFERIES, M.D.*
11:00-11:30	.	Disturbances of Calcium Metabolism . . . . . PENN G. SKILLERN, M.D.
11:30-12:00	.	Iodine Metabolism and the Action of Antithyroid Drugs . . . . . BROWN M. DOBYNS, M.D.*
12:00-12:30	.	Question-and-Answer Panel

**Guest speaker.*

Afternoon Session

1:30- 2:30 . Panel Discussion: Treatment of Thyroid Disease
Moderator—E. PERRY MCCULLAGH, M.D.
GEORGE CRILE, JR., M.D.
BROWN M. DOBYNS, M.D.*
PENN G. SKILLERN, M.D.

2:30- 3:00 . Hypoglycemia-Producing Drugs . . . . . HENRY T. RICKETTS, M.D.*

3:00- 3:15 . Intermission

3:15- 3:45 . Diabetic Acidosis and Coma . . . . . HENRY T. RICKETTS, M.D.*

3:45- 4:30 . Disturbances of Adrenocortical Function . . E. PERRY MCCULLAGH, M.D.

4:30- 5:00 . Question-and-Answer Panel

Tuesday, March 26, 1957

Morning Session

Gastrointestinal Disease

8:30- 9:30 . Pathology Conference: Diseases of the Liver . . JOHN B. HAZARD, M.D.
LAWRENCE J. MCCORMACK, M.D.
HAROLD R. ROSSMILLER, M.D.
CHARLES H. BROWN, M.D.

9:30-10:00 . Needle Biopsy of the Liver. (Motion Picture Presentation) . . . . . CHARLES H. BROWN, M.D.

10:00-10:15 . Intermission

10:15-10:45 . Bile-Pigment Metabolism . . . . . HAROLD R. ROSSMILLER, M.D.

10:45-11:30 . Treatment of Chronic Liver Disease . . . . . FRANCIS J. OWENS, M.D.

11:30-12:00 . Pancreatitis, Acute and Chronic . . . . . E. N. COLLINS, M.D.

12:00-12:30 . Question-and-Answer Panel

Afternoon Session

1:30- 2:15 . Pathology Conference: Diseases of the Colon . . JOHN B. HAZARD, M.D.
LAWRENCE J. MCCORMACK, M.D.
E. N. COLLINS, M.D.
RUPERT B. TURNBULL, JR., M.D.

2:15- 2:45 . The Collagen Diseases . . . . . JOHN H. TALBOTT, M.D.*

2:45- 3:15 . Rheumatoid Arthritis . . . . . ARTHUR L. SCHERBEL, M.D.

3:15- 3:30 . Intermission

3:30- 4:00 . Gout . . . . . JOHN H. TALBOTT, M.D.*

4:00- 4:30 . Recent Developments in the Diagnosis, Treatment, and Prevention of Viral Infections . . . . . JOHN W. KING, PH.D., M.D.

4:30- 5:00 . Neuropsychiatric Aspects of Brain Injury . . . LOUIS J. KARNOSH, M.D.

5:00- 5:30 . Question-and-Answer Panel

Wednesday, March 27, 1957

Morning Session

Hematology

8:30- 9:30 . Pathology Conference: The Leukemias and Malignant Lymphomas . . . . . JOHN B. HAZARD, M.D.
LAWRENCE J. MCCORMACK, M.D.
JOHN D. BATTLE, JR., M.D.
JAMES S. HEWLETT, M.D.

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*Guest speaker.

9:30-10:00	.	Erythrocytosis, Primary and Secondary . . . . JAMES S. HEWLETT, M.D.
10:00-10:30	.	Iron Metabolism and Iron-Deficiency Anemias . JOHN W. HARRIS, M.D.*
10:30-10:45	.	Intermission
10:45-11:30	.	The Hemolytic Anemias, Hereditary and Acquired . . . . . RUSSELL WEISMAN, M.D.*
11:30-12:00	.	Disorders of Blood Coagulation . . . . . JAMES S. HEWLETT, M.D.
12:00-12:30	.	Question-and-Answer Panel

Afternoon Session

1:30- 2:00	.	The Macrocytic Anemias . . . . . TOM D. SPIES, M.D.*
2:00- 2:30	.	Erythroblastosis . . . . . VIOLA V. STARTZMAN, M.D.
2:30- 3:00	.	The Hemoglobinopathies . . . . . JOHN D. BATTLE, JR., M.D.
3:00- 3:15	.	Intermission
3:15- 3:45	.	Pathologic Physiology of Myeloma . . . . JOHN D. BATTLE, JR., M.D.
3:45- 4:30	.	Nutrition in the Prevention and Treatment of Illness. TOM D. SPIES, M.D.*
4:30- 5:00	.	Question-and-Answer Panel

Thursday, March 28, 1957

Morning Session

Cardiovascular Disease

8:30- 9:30	.	Pathology Conference: Coronary Heart Disease . . . . . LAWRENCE J. MCCORMACK, M.D. A. CARLTON ERNSTENE, M.D. WILLIAM L. PROUDFIT, M.D.
9:30-10:00	.	Diagnosis and Treatment of Segmental Arteriosclerosis Obliterans . . . . . FAY A. LEFEVRE, M.D.
10:00-10:15	.	Intermission
10:15-10:45	.	Pathogenesis of Atherosclerosis . . . . . IRVINE H. PAGE, M.D.
10:45-11:15	.	Rheumatic Fever—Pathogenesis, Treatment, and Prevention . . . . . ROBERT D. MERCER, M.D.
11:15-12:00	.	Cerebrovascular Syndromes . . . . . LOUIS J. KARNOSH, M.D.
12:00-12:30	.	Question-and-Answer Panel

Afternoon Session

1:30- 2:30	.	Pathology Conference: Congenital Heart Disease . . . . . LAWRENCE J. MCCORMACK, M.D. F. MASON SONES, JR., M.D.
2:30- 3:15	.	Newer Technics in the Diagnosis of Congenital Cardiac Anomalies . . . . . F. MASON SONES, JR., M.D.
3:15- 3:30	.	Intermission
3:30- 4:00	.	Direct-Vision Intracardiac Surgery . . . . . DONALD B. EFFLER, M.D. WILLEM J. KOLFF, M.D.
4:00- 4:45	.	Fluid and Electrolyte Balance . . . . . ARTHUR C. CORCORAN, M.D.
4:45- 5:15	.	Question-and-Answer Panel

*Guest speaker.

Friday, March 29, 1957

Morning Session

Cardiovascular and Renal Disease

8:30- 9:30	.	Pathology Conference: Renal Disease . . . . . JOHN B. HAZARD, M.D. LAWRENCE J. McCORMACK, M.D. HARRIET P. DUSTAN, M.D. DAVID C. HUMPHREY, M.D.
9:30-10:15	.	Pathogenesis of Essential Hypertension . . . . HARRY GOLDBLATT, M.D.*
10:15-10:30	.	Intermission
10:30-11:00	.	Newer Therapeutic Tools in Hypertension . . DAVID C. HUMPHREY, M.D.
11:00-11:30	.	Management of Chronic Nephritis . . . . . HARRIET P. DUSTAN, M.D.
11:30-12:00	.	The Clinical Manifestations of Functioning Carcinoid Tumors . . . . . ROLAND E. SCHNECKLOTH, M.D.
12:00-12:30	.	Question-and-Answer Panel

Afternoon Session

Cardiovascular and Pulmonary Disease

1:30- 2:00	.	The Mechanism of Edema . . . . . CARL J. WIGGERS, M.D.
2:00- 2:30	.	Use of Drugs in Heart Disease . . . . . WILLIAM L. PROUDFIT, M.D.
2:30- 3:15	.	Coronary Heart Disease . . . . . A. CARLTON ERNSTENE, M.D.
3:15- 3:30	.	Intermission
3:30- 4:00	.	Pulmonary Function Studies in Clinical Medicine . . . . . RICHARD N. WESTCOTT, M.D.
4:00- 5:00	.	Panel: Antimicrobial Therapy in Special Fields *Moderator*—HOWARD S. VAN ORDSTRAND, M.D. *Urology*—WILLIAM J. ENGEL, M.D. *Surgery*—RUPERT B. TURNBULL, JR., M.D. *Dermatology*—JOHN R. HASERICK, M.D. *Internal Medicine*—RAY A. VAN OMMEN, M.D.
5:00- 5:30	.	Question-and-Answer Panel

Affiliations of Guest Speakers

BROWN M. DOBYNS, M.D., Associate Professor of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

HARRY GOLDBLATT, M.D., Head, Department of Laboratories, Mt. Sinai Hospital, Cleveland, Ohio.

JOHN W. HARRIS, M.D., Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

WILLIAM McK. JEFFERIES, M.D., Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

HENRY T. RICKETTS, M.D., F.A.C.P., Professor of Medicine, The University of Chicago, the School of Medicine, Chicago, Illinois.

TOM D. SPIES, M.D., F.A.C.P., Director, Nutrition Clinic, Jefferson-Hillman Hospital, Birmingham, Alabama.

JOHN H. TALBOTT, M.D., F.A.C.P., Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York.

RUSSELL WEISMAN, M.D., Senior Instructor in Medicine and Clinical Pathology, Western Reserve University School of Medicine, Cleveland, Ohio.

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*Guest speaker.